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PATENT
Docket No. 56001US002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Manoj NIRMAL	) Group Art Unit:	1774
Serial No.:	09/662,980	) Examiner:	Bruce Hess
Confirmation No.:	3575	)	
Filed:	September 15, 2000	)	
For:	SELECTIVE THERMAL TRANSFER OF LIGHT EMITTING POLYMER BLENDS	)	

APPELLANTS' BRIEF ON APPEAL

Commissioner for Patents
Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is presented in support of the Appeal filed June 8, 2004, from the final rejection of claims 1-15 and 18-26 of the above-identified application under 37 C.F.R. §§1.113 and 1.191.

This Brief is being submitted in triplicate, as set forth in 37 C.F.R. §1.192(a). Please charge Deposit Account No. 13-4895 the fee for filing this Brief under 37 C.F.R. §1.17(f).

Real Party in Interest

The real party in interest of the above-identified patent application is the assignee, 3M Innovative Properties Company, as evidenced by the assignment recorded at Reel 11405, Frame 313/316.

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Related Appeals and Interferences

There are no appeals or interferences known to Appellants' Representatives that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

Status of Claims

The pending claims are claims 1-26. The Examiner objected to claims 16 and 17, but indicated that they would be allowable if rewritten in independent form. Thus, claims 16 and 17 are not under appeal. Rejected claims 1-15 and 18-26, all of which are on appeal, are listed in APPENDIX A.

Status of Amendments

No response after Final action under 37 C.F.R § 1.116 was submitted.

Summary of the Invention

With respect to the pending claims, Appellants' invention provides a selectively thermally transferable blend capable of forming the emissive layer of an organic electroluminescent device. The blend includes a light emitting polymer and an additive selected to promote selective thermal transfer of the blend from a donor element to a proximately located receptor substrate. Light emitting polymers are disclosed in the specification at, for example, page 3 lines 18-29. Additives are disclosed in the specification at, for example, page 3, line 30 to page 4, line 5.

Independent claim 1 indicates that the thermal transfer donor element comprises a substrate and a transfer layer capable of being selectively thermally transferred from the donor element, the transfer layer comprising a blend of a light emitting polymer and an additive that forms domains in the light emitting polymer, the additive being selected to promote high fidelity

thermal transfer to the transfer layer and the blend being capable of forming an emissive layer of an organic electroluminescent device (e.g., present application at page 2, lines 5-10).

In some specific embodiments (e.g., claims 5-10), the light emitting polymer comprises poly(phenylenevinylene), poly-para-phenylene, polyfluorene, a copolymer, a molecular dopant, or a fluorescent dye (e.g., present application at page 3, lines 18-29).

In some specific embodiments, the additive comprises an oligomer of the light emitting polymer (e.g., claim 11), an organic small molecule material (e.g., claim 12), an inert polymer (e.g., claim 13), a conductive polymer (e.g., claim 14), a conjugated polymer (e.g., claim 15), or polystyrene (e.g., claim 16-17) (e.g., present application at page 17, lines 5-10).

Independent claim 19 indicates a process for patterning a light emitting polymer comprising the steps of: providing a thermal transfer donor element comprising a substrate and a transfer layer comprising a blend of a light emitting polymer and an additive that forms domains in the light emitting polymer, the additive being selected to promote high fidelity thermal transfer of the transfer layer and the blend being capable of forming an emissive layer of an organic electroluminescent device; bringing the donor element into close proximity with a receptor substrate; and selectively thermally transferring portions of the transfer layer from the donor to the receptor (e.g., present application at page 2, lines 11-18).

Issue

Whether claims 1-15 and 18-26 are unpatentable under 35 U.S.C. §112, first paragraph, for lack of enablement.

Grouping of Claims

For the purposes of this appeal, claims 1-15 and 18-26 stand or fall together.

Arguments

Claims 1-15 and 18-26 were rejected under 35 U.S.C. §112, first paragraph, as being broader than the enabling disclosure. Appellants respectfully traverse the rejection, and request review and reversal by the Board.

1. THE EXAMINER HAS NOT MET HIS BURDEN OF ESTABLISHING A REASONABLE BASIS TO QUESTION WHY THE SCOPE OF PROTECTION IS NOT ADEQUATELY ENABLED BY THE DISCLOSURE.

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure)." M.P.E.P §2164.04. Furthermore, "[a]ccording to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing *In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981))." M.P.E.P §2164.04.

The present rejection is based solely on the statement that "[n]o guidance other than the use of polystyrene is given with respect to the selection of suitable additives that form domains in the light emitting polymer. Suitable additives other than polystyrene cannot be determined without undue experimentation" (e.g., page 2, lines 3-5 of Office Action mailed on 10 March 2004).

Appellants respectfully submit that the Examiner has failed to provide *any* reasons for his conclusion that "undue experimentation" would be required to select an appropriate additive.

As such, Appellants respectfully submit that the Examiner has not established a *prima facie* case of unpatentability under 35 U.S.C. §112, first paragraph.

2. THE SPECIFICATION COMPLIES WITH THE REQUIREMENTS OF THE FIRST PARAGRAPH OF 35 U.S.C. § 112 BY ENABLING ANY PERSON SKILLED IN THE ART TO MAKE AND USE THE SUBJECT MATTER DEFINED BY EACH OF THE REJECTED CLAIMS.

"Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. ... Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." M.P.E.P. §2164.01, citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Appellants respectfully submit that the specification discloses not only polystyrene, but also many other classes of compounds. The specification discloses that "[e]xamples of additives that can be used in blends of the present invention include small molecule organics (inert, conductive, light emitting), oligomers of the LEP in the blend or of different polymers (inert, conductive, conjugated), other polymers (inert, conductive, conjugated), plasticizers, tackifying resins, and others. LEP blends should include compatible materials, for example materials that are soluble in some of the same solvents and that can be coated to form a uniform film when blended" (e.g., present application, page 3, line 30 to page 4, line 5).

The specification also discloses that "[e]xamples of blends of LEPs and suitable additives include the following: LEPs blended with oligomers of the same LEP material; LEPs blended with inert polymers (e.g., polyfluorene LEPs blended with polystyrene); LEPs blended with

active polymers such as other LEPs, conductive polymers, and the like; LEPs blended with active organic small molecule materials; molecularly doped LEPs blended with suitable additives; fluorescent dye dispersed LEPs blended with suitable additives; co-polymers of LEPs blended with suitable additives; LEPs that comprise backbone polymers having active pendent groups blended with suitable additives; and the like"(e.g., page 17 lines 3-10 of present application).

Thus, Appellants respectively submit that the basis of the Examiner's rejection, i.e., that "[n]o guidance other than the use of polystyrene is given," cannot be reconciled with the disclosure in the specification.

Moreover, the specification provides further guidance for one of skill in the art to select suitable additives. For example, the specification discloses that "[t]he additive can be selected to promote thermal transfer properties, for example by reducing intra-layer cohesive energy in the transfer layer, altering average molecular weight, enhancing adhesion to the receptor upon transfer, and the like" (e.g., present application, page 3, lines 14-17). Further, the specification recites that

> the additive and LEP should be compatible. Preferably, the additive and LEP are both soluble in a solvent used to coat the blend onto donor element when making the donor, and the blend is capable of forming a uniform film when cast or coated. In some cases, it may be desirable for the additive material to form domains in the LEP material when blended. For example, the formation of micro-domains of the additive in the LEP may reduce the intra-layer cohesive strength enough to achieve high fidelity thermal transfer while also allowing the emissive layer to exhibit uniform electronic and emissive properties. Other considerations when selecting blend materials include relative amounts of LEP to additive (and other optional materials) in the blend, whether to use active materials as additives in the blend, how the additive might affect the electronic and/or emissive properties of the LEP, and the like.

(e.g., present application, page 16, lines 21 to page 17, line 2).

The present claims under appeal further recite that the additive forms domains in the light emitting polymer. The formation of domains of one material in a second material when the two

materials are blended is a phenomenon with which those skilled in the art are familiar, and the formation of domains may be readily confirmed using known analytical techniques. *See, for example*, Chen et al., *Macromolecules*, 22:159-164 (1989); Stevenson et al., *Applied Physics Letters*, 79:833-835 (2001); Amrani et al., *Macromolecules*, 13:649-653 (1980); Tao et al., *Macromolecules*, 23:3275-3283 (1990); and Pan, "Characterization Techniques for Polymer Blends," Department of Polymer Science, The University of Southern Mississippi [online] (retrieved on August 4, 2004), retrieved from the Internet: <URL: http://www.psrc.usm.edu/macrog/mpm/blends/chara.htm>. Such analytical techniques include, for example, fluorescence microscopy. In brief, the light emitting polymer will fluoresce very strongly while the additive is typically either non-fluorescent or fluoresces differently than the light emitting polymer. The boundaries of the domains can be clearly observed by the difference in fluorescence of the materials comprising the blend.

As such, Appellants respectively submit that the specification provides guidance for one of skill in the art to select suitable additives without undue experimentation, and that the present application meets the enablement requirement of 35 U.S.C. §112, first paragraph.

Conclusion

For at least the reasons presented herein above, Appellants respectfully submit that the Examiner has failed to present a *prima facie* case of unpatentability of claims 1-15 and 18-26. Review and reversal of the rejection of claims 1-15 and 18-26 are respectfully requested.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 405 459 735 US Date of Deposit: August 9, 2004
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, **Mail Stop Appeal Brief - Patents**, P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____
Name: Rachel Gagliardi-Gebau

APPENDIX A – PENDING CLAIMS ON APPEAL
Serial No.: 09/662,980
Docket No.: 56001US002

1. A thermal transfer donor element comprising a substrate and a transfer layer capable of being selectively thermally transferred from the donor element, the transfer layer comprising a blend of a light emitting polymer and an additive that forms domains in the light emitting polymer, the additive being selected to promote high fidelity thermal transfer to the transfer layer and the blend being capable of forming an emissive layer of an organic electroluminescent device.

2. The donor element of claim 1, further comprising a light-to-heat conversion layer disposed between the base substrate and the transfer layer.

3. The donor element of claim 2, further comprising an interlayer disposed between the light-to-heat conversion layer and the transfer layer.

4. The donor element of claim 1, further comprising a transfer assist layer disposed on the transfer layer so that the transfer layer is between the base substrate and the transfer assist layer.

5. The donor element of claim 1, wherein the light emitting polymer comprises a poly(phenylenevinylene).

6. The donor element of claim 1, wherein the light emitting polymer comprises a poly-para-phenylene.

7. The donor element of claim 1, wherein the light emitting polymer comprises a polyfluorene.

8. The donor element of claim 1, wherein the light emitting polymer comprises a co-polymer.

9. The donor element of claim 1, wherein the light emitting polymer includes a molecular dopant.

10. The donor element of claim 1, wherein the light emitting polymer includes a fluorescent dye.

11. The donor element of claim 1, wherein the additive comprises an oligomer of the light emitting polymer.

12. The donor element of claim 1, wherein the additive comprises an organic small molecule material.

13. The donor element of claim 1, wherein the additive comprises an inert polymer.

14. The donor element of claim 1, wherein the additive comprises a conductive polymer.

15. The donor element of claim 1, wherein the additive comprises a conjugated polymer.

18. The donor element of claim 1, wherein the transfer layer further comprises an organic charge conductive or semiconductive material disposed in a layer adjacent to the blend.

19. A process for patterning a light emitting polymer comprising the steps of:

providing a thermal transfer donor element comprising a substrate and a transfer layer comprising a blend of a light emitting polymer and an additive that forms domains in the light emitting polymer, the additive being selected to promote high fidelity thermal transfer of the

transfer layer and the blend being capable of forming an emissive layer of an organic electroluminescent device;

bringing the donor element into close proximity with a receptor substrate; and

selectively thermally transferring portions of the transfer layer from the donor to the receptor.

20. The process of claim 19, further comprising repeating the steps using another donor element comprising a substrate and a transfer layer comprising an organic light emitting material.

21. The process of claim 19, wherein the donor element further comprises a light to heat conversion layer disposed between the substrate and the transfer layer.

22. The process of claim 21, wherein the donor element further comprises an interlayer disposed between the light to heat conversion layer and the transfer layer.

23. The process of claim 19, wherein the receptor further comprises a pattern of electrodes.

24. The process of claim 23, wherein the receptor further comprises a buffer layer disposed on the pattern of electrodes.

25. The process of claim 23, wherein the receptor further comprises an active primer layer disposed on the pattern of electrodes.

26. The process of claim 25, wherein the active primer layer comprises a material that matches a material included in the blend.

1. Amrani et al., *Macromolecules*, 13:649-653 (1980).
2. *In re Bowen*, 492 F.2d 859, 181 USPQ 48 (CCPA 1974).
3. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir.1995).
4. *In re Bundy*, 642 F.2d 430, 209 USPQ 48 (CCPA 1981).
5. Chen et al., *Macromolecules*, 22:159-164 (1989).
6. M.P.E.P. §2164.01 (Eighth Edition, May 2004 revision).
7. M.P.E.P. §2164.04 (Eighth Edition, May 2004 revision).
8. Pan, "Characterization Techniques for Polymer Blends," Department of Polymer Science, The University of Southern Mississippi [online] (retrieved on August 4, 2004), retrieved from the Internet: <URL: http://www.psrc.usm.edu/macrog/mpm/blends/chara.htm>.
9. Stevenson et al., *Applied Physics Letters*, 79:833-835 (2001).
10. Tao et al., *Macromolecules*, 23:3275-3283 (1990).
11. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).
12. *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993).

Studies of Polymer Compatibility by Nonradiative Energy Transfer

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Received July 23, 1979

ABSTRACT: Polymers were prepared carrying fluorescent labels such that nonradiative energy transfer would be efficient over distances of about 2 nm. The emission spectra from blends of two polymers to which donor and acceptor chromophores, respectively, had been attached were then used to characterize the mutual interpenetration of the polymer chains. In blends of poly(methyl methacrylate) with methyl methacrylate–alkyl methacrylate copolymers, the data indicated a gradual change from compatibility to incompatibility. The fluorescence technique was found to be more sensitive to small changes of compatibility than differential scanning calorimetry. Blends of poly(ethyl methacrylate) or poly(propyl methacrylate) with methyl methacrylate–butyl methacrylate copolymers exhibited maximum compatibility when the average length of the copolymer side chains was equal to the length of the side chains in the homopolymer. The range of compositions of styrene–acrylonitrile copolymers which indicated compatibility with poly(methyl methacrylate) by the fluorescence technique was similar to that estimated earlier by other methods.

When a system contains two fluorescing chromophores such that the emission spectrum of the first (the donor) overlaps the absorption spectrum of the second (the acceptor), excitation energy absorbed by the donor can be transferred to the acceptor over considerable distances.[2] The efficiency E of this energy transfer is governed by the relation[2,3]

$$E = R_0^6/(R_0^6 + r^6)$$

$$R_0^6 = (8.8 \times 10^{-25})Jn^{-4}\kappa^2\Phi_D^0 \quad (1)$$

where r is the distance between donor and acceptor, R_0 is a characteristic distance at which half of the excitation energy is transferred, J is the overlap integral between the emission spectrum of the donor and the absorption spectrum of the acceptor, n is the refractive index, κ^2 is a function of the mutual orientation of the donor and acceptor transition moments, and Φ_D^0 is the fluorescence quantum yield of the donor in the absence of the acceptor.

Nonradiative energy transfer has been used extensively to characterize intramolecular distances in biological macromolecules.[3,4] A number of studies have also been reported dealing with intramolecular energy transfer in synthetic oligomers or polymers,[5] but we know of no previous study dealing with intermolecular energy transfer between two polymers labeled with donor and acceptor chromophores, respectively. In the present investigation we used this phenomenon as an experimental tool to study the compatibility of mixed chromophore-labeled polymers in bulk. It was expected that phase separation would lead to a large increase in the distances between the donors and the acceptors, reducing substantially the efficiency of energy transfer.

Experimental Section

Monomer and Analogue Preparations. 1-(2-Anthryl)ethanol was prepared as described by Etienne et al.[6] (mp 164 °C (lit.[7] mp 162–163 °C)) and 1-(2-naphthyl)ethanol (mp 76 °C (lit.[8] mp 71–72 °C)) was obtained by an analogous procedure from 2-acetylnaphthalene (Pfaltz and Bauer) recrystallized from ethanol (mp 56 °C (lit.[9] mp 56 °C)). 9-Anthrylmethanol was obtained from the Aldrich Chemical Co. *N*-(2-Hydroxyethyl)carbazole (mp 82–83 °C (lit.[10] mp 82–83 °C)) was prepared from carbazole and ethylene oxide in the presence of sodium hydroxide by the procedure of Lopatinskii et al.[10] These alcohols were converted by methacryloyl chloride to 1-(2-anthryl)ethyl methacrylate (AEMA) (mp 161 °C (lit.[7] mp 161 °C)), 1-(2-naphthyl)ethyl methacrylate (NEMA) (mp 52 °C), 9-anthrylmethyl methacrylate (mp 86–87 °C) (AMMA) and 2-(*N*-carbazolyl)ethyl methacrylate (CEMA) (mp 82.5–4 °C). The corresponding acetates, used as low molecular weight analogues of the fluorescing residues in the copolymers, were 1-(2-anthryl)ethyl acetate (AEA) (mp 140–141 °C (lit.[7] mp 140–141 °C)), 1-(2-naphthyl)ethyl acetate (NEA) (liquid at room temperature), 9-anthrylmethyl acetate (AMA) (mp 110–111 °C) and 2-(*N*-carbazolyl)ethyl acetate (CEA) (mp 69–71 °C).

Polymerization and Polymer Characterization. Polymerizations were carried to low conversion at 60 °C, using azobis(isobutyronitrile) initiator (0.1% on the weight of the monomer). The concentration of the chromophore-carrying methacrylate residues in the polymers was determined assuming that their extinction coefficients were the same as those of the corresponding acetates (cf. Table I). In the copolymerization of methyl methacrylate (MMA) with AEMA and NEMA, no significant difference was found in the composition of the polymer and monomer mixture, and it was assumed that terpolymers containing two alkyl methacrylates also contained their residues in the same proportion as the monomer mixture from which they were derived. The composition of styrene–acrylonitrile copolymers was determined by IR spectroscopy, using methylene chloride solutions and the absorbance at 2240 cm^{-1} as a measure of the concentration of nitrile groups, with isobutyronitrile as a reference standard. Molecular weights of the polymers were characterized by intrinsic viscosity (specified in the legends to the graphs in units of dL/g).

Film Casting. Films were cast from 10% tetrahydrofuran or methylene chloride solutions containing equal concentrations of two polymers carrying donor and acceptor fluorescent labels, respectively, onto Teflon plates after removal of dissolved gases by exposure of the solution to a reduced pressure. The solvent was allowed to evaporate slowly for 2 days at room temperature in a nitrogen atmosphere and the films were then dried for a day in a vacuum oven at 50 °C. They were stored under vacuum up to the time of fluorescence measurements to avoid fluorescence quenching by oxygen. In the study of blends of poly(methyl methacrylate) with alkyl methacrylate copolymers, the film thickness was held to 0.035 ± 0.005 mm. In later experiments, a film thickness of 0.015 ± 0.005 mm was used.

Fluorescence Measurements. Emission spectra were recorded on a Hitachi-Elmer MPF-2A spectrophotometer equipped with a 150 W xenon lamp, a R 106 photomultiplier, and a PQD recorder. For the determination of reflectance fluorescence spectra, films were mounted between quartz plates with the exciting beam at 60° and the observation of the emission at 30° to the sample surface.

Glass Transition Measurements. The glass transitions of polymer films were determined by using a DuPont thermal analyzer 900 modified with a 900693 rebuilt DSC cell. The polymer sample and an empty reference pan were heated at a rate of 10 °C/min up to 140 °C. The sample was then rapidly quenched in dry ice and the thermal behavior was recorded from 0 to 130 °C under nitrogen.

0024-9297/80/2213-0649$01.00/0 © 1980 American Chemical Society

Table I
Spectroscopic Data for Donor-Acceptor Pairs

compd	λ_{ex}, nm	λ_{max}, nm	$10^3\epsilon_{ex}$, M^{-1} cm^{-1}	$10^3\epsilon_{max}$, M^{-1} cm^{-1}	λ_{em}, nm	$10^{35}J$,[12] cm^6 mol^{-1}	$\Phi_D{}^0$ [13]	R_0, nm
NEA	276	276	5.2	5.2	336	5.13	0.13	1.9-2.0
AEA	276	357	1.16	6.5	408			
CEA	296	296	15.4	15.4	347	9.07	0.69	2.7-2.9
AMA	296	386	0.60	8.8	413			

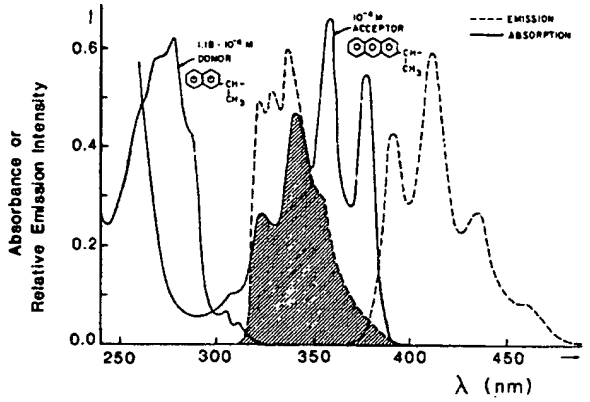


Figure 1. Absorption and emission spectra of NEA and AEA. The overlap integral is crosshatched.

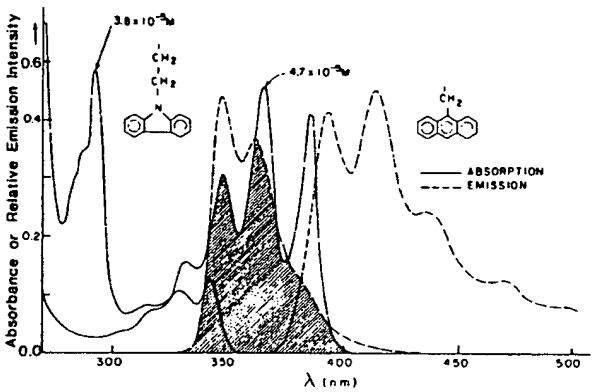
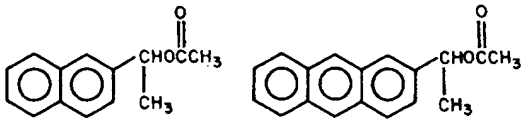


Figure 2. Absorption and emission spectra of CEA and AMA. The overlap integral is crosshatched.

Results and Discussion

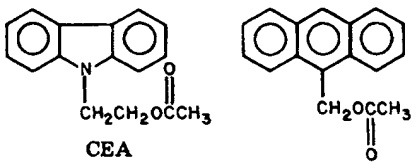
Characterization of Chromophore Labels. For chromophore labels appended to polymers for studies of compatibility by nonradiative energy transfer, the product of the overlap integral J between the donor emission and the acceptor absorption spectrum and of the donor fluorescence quantum yield $\Phi_D{}^0$ must be sufficiently large to yield a characteristic distance, R_0, for energy transfer not less than about 2 nm. In the present study two methacrylate derivative pairs carrying donor and acceptor chromophores were employed as comonomers to introduce the labels into the polymers. The corresponding acetates, with structures given below, were used to determine their

donor-acceptor pair I



NEA AEA

donor-acceptor pair II



CEA AMA

spectroscopic characteristics. These are given in Table I, which lists the excitation wavelength, λ_{ex}, with the molar extinction coefficients of the donor and of the acceptor, ϵ_{ex} and ϵ_{max}, at the excitation wavelengths and the absorption maximum, respectively, wavelength λ_{em} of the emission maxima of donor and acceptor, $\Phi_D{}^0$, J, and R_0. A value of $\kappa^2 = 0.476$ (corresponding to a random orientation of donor and acceptor in a rigid medium[11]) and n values ranging from 1.48 for poly(butyl methacrylate) and $n = 1.59$, for polystyrene, were used in calculating R_0. The absorption and emission spectra of the two donor-acceptor pairs are shown in Figures 1 and 2.

In the initial study, involving mixtures of poly(methyl methacrylate) (PMMA) with methyl methacrylate-ethyl methacrylate (MMA-EMA) and methyl methacrylate-butyl methacrylate (MMA-BMA) copolymers, the comonomers NEMA and AEMA were employed to introduce the fluorescent labels. In later investigations, we used for this purpose the donor-acceptor pair CEMA-AMMA, which is characterized by a larger $J\Phi_D{}^0$ [12,13] and has the advantage that it can be excited at 296 nm, a wavelength at which styrene copolymers have no significant absorption.

Energy Transfer between PMMA and Methyl Methacrylate Copolymers.[14] In a blend containing a mixture of a donor-labeled polymer and an acceptor-labeled polymer, energy transfer would be expected to be favored if the two polymeric species can freely interpenetrate one another in a single phase. On the other hand, if the system separates into two phases, energy transfer will only be possible in the neighborhood of the phase boundary. Thus, the emission spectrum from such a blend should contain information concerning the compatibility of the two polymeric species. To evaluate the utility of this method, we determined the ratio I_N/I_A of the emission intensities at the λ_{em} wavelengths of the naphthyl and anthryl groups in films containing equal weights of a terpolymer of methyl methacrylate with ethyl or butyl methacrylate and 1.2 wt % of NEMA and a copolymer of methyl methacrylate with 1.4 wt % of AEMA. The results plotted in Figure 3 show that this ratio increases, corresponding to a decreasing energy transfer, as the ethyl or butyl methacrylate content of the copolymer is increased but levels off to a constant value for blends in which the copolymer contains less than 60 mol % of methyl methacrylate. The fluorescence spectra thus reflect the decreasing compatibility of the two components of the blend, leading eventually to a two-phase system. Three features of the results deserve special notice.

(1) The data suggest that the transition from compatibility to incompatibility occurs gradually over a broad range of the copolymer composition. This is in sharp contrast to results obtained by Fried et al.[15] in a differential

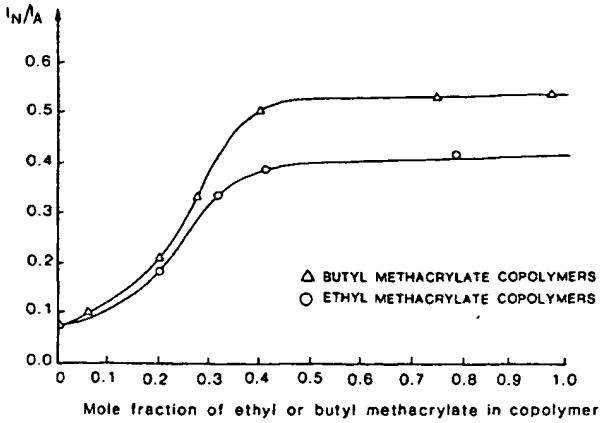


Figure 3. Ratio of donor and acceptor fluorescence intensities in films containing equal weights of donor-labeled methyl methacrylate–ethyl methacrylate or methyl methacrylate–butyl methacrylate copolymers ($[\eta]_{25}$ = 2.2–2.4 in dioxane) and acceptor-labeled poly(methyl methacrylate) ($[\eta]$ = 2.0 in dioxane).

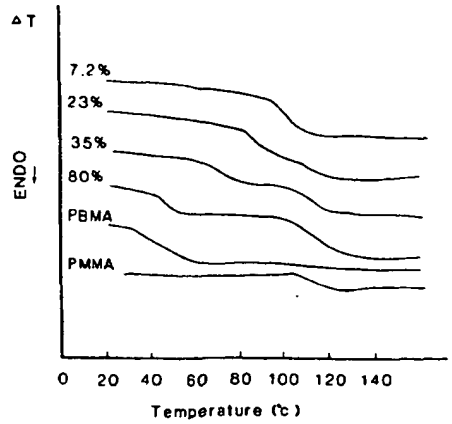


Figure 4. DSC traces of poly(methyl methacrylate), poly(butyl methacrylate), and mixtures of equal weights of PMMA with methyl methacrylate–butyl methacrylate copolymers. The numbers specify the mole percent of butyl methacrylate residues in the copolymer.

scanning calorimeter (DSC) study of blends of poly(2,6-dimethyl-1,4-phenylene oxide) with styrene–4-chlorostyrene copolymers. This study indicated that the transition from a one-phase to a two-phase behavior occurs sharply at a critical concentration of the copolymer. As will be shown later, glass transition phenomena, as reflected in the calorimetric behavior of polymer blends, are much less sensitive than energy transfer between polymer-bound chromophore label in revealing the mutual interpenetration of polymer chains.

(2) When the solutions of NEA and AEA with the same optical density at the excitation wavelength of 276 nm were irradiated, the ratio of the fluorescence intensities at 336 and 408 nm was 0.87. Since the ratio of the molar extinction coefficients of these species at 276 nm is 4.48 and the ratio of the molar concentration of donors and acceptors in the polymer blend is 1.04, a ratio $I_N/I_A = 4.7$ would be expected in the absence of energy transfer. It may be seen on Figure 3 that I_N/I_A values actually observed in the plateau region are lower by an order of magnitude. This suggests that we must be dealing in the two-phase systems with extremely small phase domains.

(3) It was expected that incompatibility with PMMA would require a larger content of ethyl methacrylate than butyl methacrylate in the copolymer. This was not observed. Figure 3 shows that the plateau region is attained at the same comonomer content in the two systems. The somewhat larger energy transfer characterizing the two-phase systems containing ethyl methacrylate copolymers may reflect a smaller interfacial energy leading to an increased interfacial area.

DSC Studies of Blends of PMMA with Methyl Methacrylate Copolymers. DSC traces of PMMA, poly(butyl methacrylate), and blends of PMMA with methyl methacrylate–butyl methacrylate (BMA) copolymers are shown on Figure 4. The blends containing copolymers with 80 and 35 mol % of BMA reveal two glass transitions. The double T_g is less evident in the blend in which the copolymer contains 23 mol % of BMA and is totally absent in a blend with a copolymer containing 7.2 mol % of BMA. Thus, DSC is unable to reveal the less intimate mixing which results when two components of a blend differ only slightly in their composition. Also, DSC results would class a blend as containing two phases before the plateau region is reached in the fluorescence characteristics of the chromophore labeled polymer blends. Similar conclusions were arrived at in DSC studies of blends of PMMA with methyl methacrylate–ethyl methacrylate copolymers and a comparison with fluorescence data on these systems.

Past studies have shown that measurements of dynamic mechanical properties are more sensitive to the separation of polymer blends into two phases than DSC measurements[16] and that electron microscopy can detect even smaller domains in a two-phase system.[17] It would be most desirable to compare in the future results obtained by these two techniques with those obtainable by fluorimetry.

Energy Transfer between Poly(ethyl methacrylate) or Poly(propyl methacrylate) with Methyl Methacrylate–Butyl Methacrylate Copolymers. In the absence of specific molecular interactions such as hydrogen bonding, it would be expected that a matching of cohesive energy densities would be the appropriate condition necessary to arrive at compatible polymer blends. A particularly simple system on which this assumption can be tested would consist of an alkyl methacrylate homopolymer and alkyl methacrylate copolymers. If the cohesive energy is the sum of contributions from chemical groups constituting a polymer, as has been demonstrated by a number of investigators,[18] then a methacrylate homopolymer and a methacrylate copolymer should be miscible if the mean length of the copolymer side chains matches the length of the homopolymer side chains. Fluorescence data obtained with blends of poly(ethyl methacrylate) or poly(propyl methacrylate) with methyl methacrylate–butyl methacrylate copolymers are plotted in Figure 5. It may be seen that the ratio of the emission intensities of the CEMA and AMMA residues, I_C/I_A, passes through a minimum with mole fractions of 1/3 and 2/3 butyl methacrylate in the copolymers when they are blended with poly(ethyl methacrylate) and poly(propyl methacrylate), respectively. This is precisely the point of maximum compatibility predicted from cohesive energy density considerations.

Energy Transfer between Poly(methyl methacrylate) and Styrene–Acrylonitrile Copolymers (S–AN). This system is of special interest since compatibilities have previously been studied by a number of techniques.[19] Solutions of styrene–acrylonitrile copolymers in poly(methyl methacrylate) have also been investigated by neutron scattering.[20] Plots of I_C/I_A for blends of PMMA with S–AN of varying composition are shown in Figure 6 for two PMMA samples of different molecular weight. As would be expected, an increasing molecular weight renders compatibility more difficult. Nevertheless,

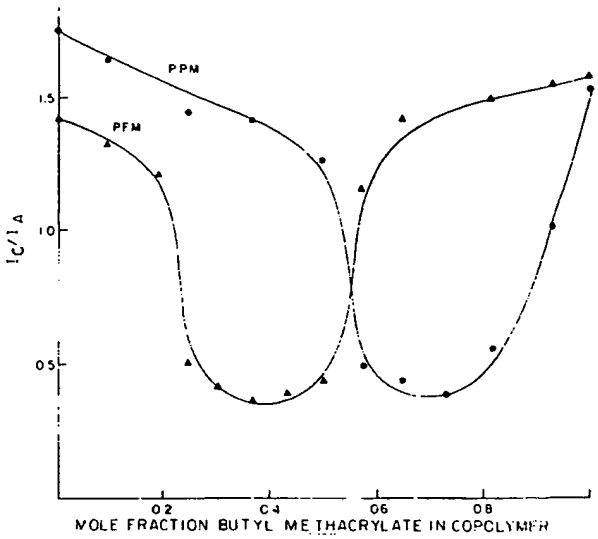


Figure 5. Ratio of donor and acceptor fluorescence intensities in films containing equal weights of poly(ethyl methacrylate) (PEM, $[\eta]_{30}$ = 1.24) or poly(propyl methacrylate) (PPM, $[\eta]_{30}$ = 1.35) labeled with 1.1 wt % of AMMA and a methyl methacrylate–butyl methacrylate copolymer labeled with 0.8 wt % of CEMA ($[\eta]_{30}$ = 0.6–0.8 in benzene).

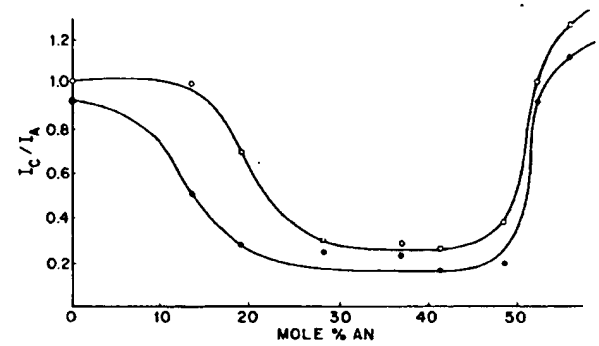


Figure 6. Ratio of donor and acceptor fluorescence intensities in films containing equal weights of styrene–acrylonitrile copolymers labeled with 1.45 wt % of CEMA and poly(methyl methacrylate) labeled with AMMA: (○) $[\eta]_{PMMA}$ = 1.06, 0.91 wt % AMMA; (●) $[\eta]_{PMMA}$ = 0.18, 1.00 wt % AMMA. The $[\eta]$ were measured in benzene at 25 °C; for the copolymers they increased with increasing acrylonitrile content from 0.51 to 0.97.

it is surprising that the I_C/I_A minimum is distinctly higher with the longer PMMA, suggesting that the interpenetration with S–AN is somehow less perfect even when the compatibility of the two materials has been optimized.[21] It should also be noted that the range of compatibility which lies according to Stein et al.[19] between 16 and 42 mol % of acrylonitrile in the copolymer is located more narrowly by the fluorescence technique.

Concluding Remarks. This investigation has shown that energy transfer between polymers labeled with donor and acceptor chromophores provides a powerful tool for the study of polymer compatibility. It should be noted, however, that changes in the ratio of donor and acceptor fluorescence intensity do not define uniquely the distribution of the macromolecular species. This ratio should, in fact, be sensitive both to the size and the geometry of phase domains.

One of the most striking features of our results is the apparently gradual transition from a two-phase to a one-phase behavior. At least four different interpretations for such a gradual change can be thought of: (1) Since the polymers are polydisperse, incompatibility may gradually extend to lower molecular weight fractions. (2) The phase boundary may not be sharp, and the depth to which polymers contained in one phase penetrate into the other may gradually decrease. "Fuzzy" phase boundaries between two polymers have, in fact, been observed both by electron microscopy[22] and phase-contrast microscopy.[23] (3) A gradually decreasing energy transfer may reflect a decrease in the interfacial area due to an increase in the interfacial energy. (4) Composition fluctuation may appear on a microscopic scale, although no phase separation is involved. Such phenomena were observed by electron microscopy[24] and by pulsed NMR[25] in blends which appeared homogeneous by the usual diagnostic criteria. Although such phenomena are revealed by these methods, the technique we have used recommends itself by its great experimental simplicity.

Acknowledgment. One of us (F.A.) thanks the American Friends of the Middle East for financial support during this study, and we are grateful to Dr. F. Mikeš for his critical reading of our manuscript. We are indebted for sponsorship of this investigation to the National Science Foundation under their Grant No. DMR 77-05210, Polymers Program.

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(12) These values were obtained without correcting the experimental emission spectra for the wavelength dependence of the fluorimeter sensitivity. It was confirmed that the error thus introduced is minor since the overlap integral is largely determined by the emission intensity of the donor in a narrow spectral range. It may be noted that the J value for the CEA–AMA pair is identical with that given by I. B. Berlman for the *N*-methylcarbazole–9-methylanthracene pair ("Energy Transfer Parameters of Aromatic Molecules", Academic Press, New York, 1973, p 208).
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Synthesis and Investigation of Macrocyclic Polystyrene‡

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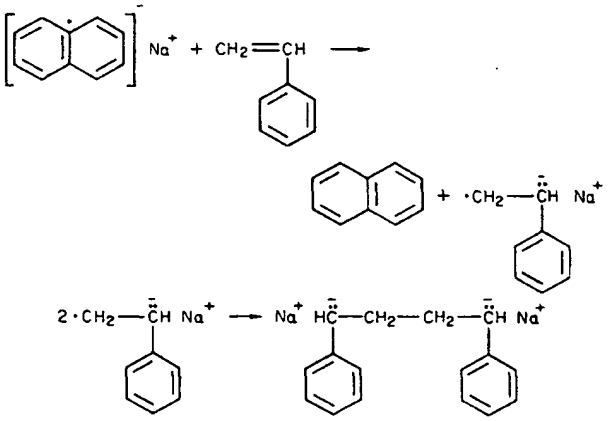
ABSTRACT: Macrocyclic polystyrene samples (30 < DP < 250) with narrow molecular weight distribution have been prepared by living bifunctional anionic polymerization and by coupling with α,α'-dichloro-*p*-xylene. The polymers have been investigated by gel permeation chromatography and viscosity measurements. The GPC data of both cyclic and acyclic polymers fulfill the Benoit relationship. The ratio of the intrinsic viscosity of ring and linear polymer chains was found to be close to 0.65 in cyclohexane at 34.5 °C. In toluene at 25 °C it is a function of the molecular weight ($0.56 < [\eta]_r/[\eta]_l < 0.76$).

A broad variety of circular DNA has been observed in the past,[1-3] proving the high biological importance of ring-shaped molecules.

On the other hand a number of theoretical studies have appeared treating the hydrodynamic properties of cyclic macromolecules in comparison with linear molecules of the same molecular weight.

Reports on synthetic cyclic polymers occur only sporadically in the literature. Semlyen et al.[4] described the preparation and characterization of cyclic poly(dimethylsiloxane) $[(CH_3)_2SiO]_x$ and Jones[5] reported on cyclics in styrene–dimethylsiloxane block copolymers.

In the present paper we describe a method for the preparation of cyclic polystyrene by anionic polymerization using sodium naphthalene as an initiator[6] which generates a bifunctional "living" chain and α,α'-dichloro-*p*-xylene



as a bifunctional terminating agent. Linear and cyclic molecules were separated by fractionation after reaction of the linear molecules having chlorine end groups with high molecular weight living polystyrene.

The cyclic polymers with narrow (nearly Poisson) molecular weight distribution have been characterized by gel permeation chromatography and by viscosity.

Experimental Section

1. Materials. Inert gases (N_2, Ar) were purified by passing them through columns filled with Al_2O_3 as a support for metallic potassium and bubbling them through a solution of α-methylstyrylsodium.

Tetrahydropyran was refluxed over K and fractionated. Then it was stored over potassium benzophenone ketyl and distilled off before use.

Naphthalene was purified by sublimation.

α,α'-Dichloro-*p*-xylene (Schuchardt, Munich) was recrystallized from ethanol and sublimated in N_2 atmosphere. The melting point of the pure product was 100 °C.

Styrene was purified in the usual manner. Before use it was distilled from $LiAlH_4$.

2. Preparation of Polystyrene and Cyclization. The apparatus for polymerization and cyclization reactions is shown in Figure 1. It was heated in vacuo with a flame and then filled with Ar. From the 2-L flask A containing tetrahydropyran (THP) as a solvent and the tetrameric dianion of α-methylstyrene with Na^+ as the gegenion, THP was distilled into the 2-L flask B in vacuo. Via tube k all flasks can be filled with pure THP. In flask C the initiator, sodium naphthalene, was prepared in THP. From flask F containing styrene and $LiAlH_4$, styrene was distilled in vacuo into flask E. In flask D the polymerization of styrene (0.07 mol, dissolved in 500 mL of THP) initiated by sodium naphthalene (the amount calculated to achieve a certain degree of polymerization) took place. Half of the living solution was taken off via tube l and protonated by means of methanol to yield an acyclic polystyrene sample. The other half was added dropwise and simultaneously with an equimolar amount of α,α'-dichloro-*p*-xylene dissolved in 250 mL of THP (flask H) to 1 L of pure THP (flask G) where cyclization took place. At the end of the reaction an excess of dichloro compound was added to provide all residual open chain species to carry Cl end groups.

3. Separation of Macrocycles and Acyclic Material. The material obtained after the cyclization reaction was freeze-dried, dissolved in 100 mL of THP, and reacted with high molecular weight ($50\,000 < M < 200\,000$) living polystyrene prepared with a bifunctional initiator in THP solution which was added dropwise

† Part of her Ph.D. Thesis.
* Dedicated to Professor P. J. Flory on the occasion of his 70th birthday with very best wishes.

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In re BOWEN

(CCPA)
181 USPQ 48
Decided Feb. 28, 1974
No. 9135
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Pleading and practice in Patent Office — Rejections (§ 54.7)

Specification — Sufficiency of disclosure (§ 62.7)

Even in cases involving unpredictable world of chemistry, Patent Office, in holding that application does not comply with enablement portion of first paragraph of 35 U.S.C. 112, must give reasons why it considers that it is uncertain that class of materials will work in claimed process in contravention to application's statement that invention, in its broader aspects, is applicable to materials other than those disclosed as operative in claimed process.

2. Amendments to patent application — New matter (§ 13.5)

Interference — Reduction to practice — Constructive reduction (§ 41.755)

Specification — Sufficiency of disclosure (§ 62.7)

Description requirement of first paragraph of 35 U.S.C. 112 serves essentially two functions; in the simple case, where no prior application is relied upon, requirement is that invention claimed be described in specification as filed; as such, a rejection on requirement is tantamount to a new matter rejection under section 132; both are defeated by a specification which describes invention in same terms as claims; in another situation, where benefit of prior application is claimed under section 120, requirement mandates a description of invention, which is claimed in later-filed case, in specification of application relied upon for support under statute.

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Particular patents—Filter
Bowen, Polymerization Pre-Filter, claims 1 and 3 to 11 of application allowed.

Case History and Disposition:

Appeal from Board of Appeals of the Patent Office.
Application for patent of David Bowen, Jr., Serial No. 766,192, filed Oct. 9, 1968; Patent Office Group 140. From decision rejecting claims 1 and 3 to 11, applicant appeals. Reversed.

Attorneys:

STANLEY M. TARTER (KELLY O. CORLEY of counsel) both of Pensacola, Fla., for appellant.

JOSEPH F. NAKAMURA (JACK E. ARMORE of counsel) for Commissioner of Patents.

Judge:

Before MARKEY, Chief Judge, and RICH, BALDWIN, LANE, and MILLER, Associate Judges.

Opinion Text

Opinion By:

RICH, Judge.

This appeal is from the decision of the Patent Office Board of Appeals, adhered to on reconsideration, affirming the rejection under 35 U.S.C. 112 of claims 1 and 3-11 of application serial No. 766,192, filed October 9, 1968, entitled "Polymerization Pre-Filter." The board stated under Rule 196(c) that, in the absence of a new ground of rejection, claim 2 would be allowed if rewritten in independent form with changes indicated by the board, and appellant has apparently filed an amendment complying with the board's statement, thus placing claim 2 in condition for allowance. We reverse as to claims 1 and 3-11.

The Invention

The invention relates to the removal of agglomerates of delusterants and other finely-divided solid powders, referred to as "pigment," from polymers by filtration at the optimum time. The pigment agglomerates, which tend to foul the spinning filter used to spin filaments from the polymer, are removed by filtering the polymerization mass before

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its viscosity has exceeded 400 poises, and preferably at considerably lower viscosities. As appellant explains, "Removal at this time can be achieved with simple equipment at relatively low pumping pressures and with a minimum power consumption, resulting in substantially increased service life for the subsequent final spinning filters." The specification discloses the use of the invention in particular processes and apparatus where the polymer is nylon 66, but notes that "in its broader aspects it is applicable to other specific processes and to other polymers."

Claim 1 is treated by both appellant and the solicitor as representative of all the appealed claims. It reads:

> 1. A polymerization process comprising:
>
> (a) introducing melt-polymerizable material having a viscosity less than 400 poises and finely divided pigment into a polymerization vessel, said pigment tending to form agglomerates under melt polymerizing conditions;
>
> (b) maintaining melt polymerizing conditions in said vessel; and
>
> (c) while polymerization is proceeding and before the viscosity of said material exceeds 400 poises:
>
> (1) pre-filtering at least a portion of said material through a pre-filter having a given rating for removal of agglomerates larger than said rating; and
>
> (2) continuing melt polymerization of said filtered portion.

The claims may be read as though the term "melt" has been cancelled in every occurrence, since appellant has apparently filed an amendment deleting "melt" wherever it appears in the claims in response to the board's criticism of the term as new matter with an indication that appellant should cancel the term.

The Rejection

The sole rejection affirmed by the board was "on the grounds that the term 'polymerizable material' is not disclosed in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains to make and use the same (35 U.S.C. 112, paragraph one)." The Examiner's Answer stated only the following as the reason for the failure of the specification to comply with the stated statutory requirement:

> The recited "polymerizable material" is not disclosed in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains to make and use same.
>
> Applicant has disclosed one specie [sic] of polyamide, i.e., polyhexamethylene adipamide, which alone is insufficient to support such a broad genus. See In re Shokal et al., 1957 C.D. 234, 113 USPQ 283 ; General Electric Co. v. Wabash Co., 37 USPQ 468 .

The board, amplifying the examiner's reasoning, stated the following as the basis for the rejection:

> The specific disclosure is drawn to polymerization in an aqueous suspension of certain nylon intermediates only. There is no suggestion that all other polymers can be employed. The nylon components are not representative of all "polymerizable materials," whatever that is intended to include. Not only are all of the very many organic polymers included but also inorganic polymers,

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which are not even suggested in the specification.

And, on reconsideration, the board, apparently agreeing with appellant's observation "that there is nothing of record to indicate that one skilled in the art could not use appellant's process in polymerizing any polymer," stated that:

> However, neither is there any evidence that polymerizable materials other than nylon intermediates will be operable in the claimed process. In our opinion, the situation here is readily distinguishable from the facts of the Burke, [25 CCPA 795, 93 F.2d 50, 36 USPQ 64 (1937),] Roberts, [113 USPQ 205 (Pat. Off. Bd. App., 1956),] Donahey, [126 USPQ 61 (Pat. Off. Bd. App., 1959), and Marzocchi, [58 CCPA 1069, 439 F.2d 220, 169 USPQ 367 (1971)] cases cited by the appellant. The properties of "polymerizable materials" can vary over a wide range, rendering it quite uncertain as to whether or not the claimed process is broadly applicable to all such materials. In the absence of such a teaching, we must agree with the examiner's rejection in this instance.

The solicitor, zeroing in on specific portions of § 112, first paragraph, quoting from this court's opinion in In re Marzocchi, 58 CCPA 1069, 1073, 439 F.2d 220, 223, 169 USPQ 367, 369 (1971), states that the specification disclosure does not contain "a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the .

subject matter sought to be patented" and hence is not in compliance "with the enabling requirement of the first paragraph of § 112." In addition, the solicitor seeks to state an additional basis under paragraph one in saying that, "consonant with the general position implicit below, there is a 'failure of the specification to meet the description requirement of the first paragraph of 35 U.S.C. 112 as to the broad claims on appeal'; In re DiLeone, 58 CCPA 934, 935, 436 F.2d 1033," 1034, 168 USPQ 598 (1971).

Opinion

§ 112, Paragraph One—Enablement

It is apparent from the language of the board that the rejection is based on the enablement portion of the first paragraph of § 112 which, as we have held, "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Whether, in a particular case, the requisite "reasonable correlation" between the scope of claims and the scope of enablement provided by the specification exists is often a difficult question. Compounded here with the resolution of that question, which requires a factual inquiry into the knowledge of persons of ordinary skill in the particular art, is the question whether, under the circumstances of this case, the applicant ought to bear the burden of coming forward with evidence to prove enablement—or whether the examiner should have the burden of coming forward with evidence to disprove it—when "there is nothing of record to indicate that one skilled in the art could not use appellant's process in polymerizing any polymer," and "neither is there any evidence that polymerizable materials other than nylon intermediates will be operable in the claimed process."

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The board resolved the latter question against appellant, giving as its reasons the general assertion that the "properties of 'polymerizable materials' can vary over a wide range, rendering it quite uncertain as to whether or not the claimed process is broadly applicable to all such materials." The board appears to have based its assertion on its own knowledge of polymer chemistry. Throughout the prosecution, appellant has advanced the theory that his "invention is a purely mechanical filtering process, and is not dependent on the chemical composition of the polymerizable material * * * temperature, pressure, or on any process conditions other than the viscosity of the reaction mass." Appellant further argued:

> It appears that the examiner is extending the chemical exception to the general rule on disclosure well beyond proper limits. The general rule on adequacy of disclosure is that disclosure of a single species is adequate support for a generic claim. An exception to the general rule has arisen in chemical cases because of the uncertainty of various chemical reactions. However, this exception is properly limited only to cases involving chemical compositions or reactions.

To the extent that there may be a difference in the resolution of the question whether enablement is accomplished when the Patent Office has not shown the *inability* of one skilled in the art to use the invention as broadly as it is claimed and appellant has not shown that materials other than those he discloses will operate in the claimed process, we do not think it hinges on whether the case is denominated "chemical" or "mechanical." Compare In re Cook, 58 CCPA 1049, 439 F.2d 730, 169 USPQ 298 (1971), with In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367 (1971), the latter being a so-called "chemical case" where enablement was found to exist, and the former being a so-called "mechanical" case where the court held enablement not accomplished. As we said in Cook, 58 CCPA at 1054, 439 F.2d at 734, 169 USPQ at 301, we would prefer to see the dichotomy which lawyers find in the chemical and mechanical cases "denominated a dichotomy between predictable and unpredictable factors in the art." However, we recognize that the realities of chemical cases often result in unpredictability. As we explained in In re Fisher, 57 CCPA at 1108, 427 F.2d at 839, 166 USPQ at 24:

> In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

[1] It is clear from the decision of the board that the unpredictability which it noted was in the admittedly chemical fact that the "properties of 'polymerizable materials' can vary over a wide range," but no reasons were given to appellant by the Patent Office for the alleged failure—or at least uncertainty—of the class of "polymerizable materials" to work in the claimed process to controvert the statement in appellant's application that his invention, in its broader aspects, is applicable to other

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polymers. See In re Nguyen Dinh-Nguyen, 181 USPQ 46 , Patent Appeal No. 9134, decided concurrently herewith. It is clear that even in cases involving the unpredictable world of chemistry such reasons are required. As we stated in In re Marzocchi, 58 CCPA at 1073, 439 F.2d at 223-24, 169 USPQ at 369-70:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Here the only reason given appellant why his specification does not enable one skilled in the art to use his invention as broadly as it is claimed is the statement of the board that "polymerizable materials" include "Not only * * * all of the very many organic polymers * * * but also inorganic polymers." But even this statement only identifies a subgenus of "polymerizable materials" without giving a reason for the implication inherent therein that inorganic polymers would not work in appellant's process. Appellant correctly notes:

> The Board of Appeals mentions "inorganic polymers", presumably intending to refer to something like the various polymers of silicon. Appellant knows of no reason why the filtration step could not be applied to such materials, nor has the Board of Appeals suggested any recognized scientific principle which would be violated in such a case.

The solicitor, possibly recognizing this deficiency, gives the first real explanation of why he doubts the truth of appellant's assertion that his invention is practicable with all polymerizable materials. He says:

> For example, it can be readily recognized that some polymerizable

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> materials, or some polymerizable materials under certain polymerizing conditions, will polymerize so quickly to a higher molecular weight polymer with a viscosity above 400 poises (also containing some agglomerated pigment) that there is no opportunity to prefilter before the viscosity exceeds 400 poises.

And, in a thirty-three line footnote at the end of the above quotation the solicitor lists several such fast "polymerizable materials" with appropriate textbook authorities.

We think, however, as we stated in a similar context in In re Barr, 58 CCPA 1388, 1401, 444 F.2d 588, 596, 170 USPQ 330, 338 (1971), that "the filing of the solicitor's brief is far too late a point in prosecution to inform an applicant of what additional working examples are thought to be needed to support his claims" or, stated another way, what materials covered by the claims allegedly would not work in the invention as claimed.

Here, however, we fail to see how even the rapid polymerizable materials identified by the solicitor (1) are covered by appellant's claims which require the pre-filtering "while polymerization is proceeding and before the viscosity of said material exceeds 400 poises," or (2) if they are within the claim, why one skilled in the art would not immediately appreciate that they are not suitable for use in the process. See In re Skrivan, 57 CCPA 1201, 427 F.2d 801, 166 USPQ 85 (1970); In re Cook, supra; and In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

Accordingly, there appears to be no basis for the non-enablement rejection on the theory that claims read on undisclosed polymers. While the claims literally comprehend numerous polymers in addition to the one specifically described in appellant's specification, nylon 66, no persuasive reason has been given by the Patent Office why the specification does not

realistically enable one skilled in the art to practice the invention as broadly as it is claimed.

Finally, the solicitor takes the position that there is another basis for lack of enablement here since appellant's disclosure is limited to "polymerizable materials" capable of producing fiber-forming polymers while the claims are not so limited. The solicitor finds this limitation implicit in the specification where appellant explains the function of his filtering process in removing the agglomerates which "foul the spinning filter normally provided just before the spinneret," the last word representing the device from which the polymer fibers are drawn. The solicitor asserts that the board and the examiner "clearly indicated that appellant's effective disclosure in the specification appears to be limited to certain nylon polyamides (which cannot reasonably be considered to be representative of *all* polymerizable materials)—that are in fact *fiber-forming* polymers," citing portions of the Examiner's Answer and the board's opinion wherein *other rejections, reversed by the board,* were discussed. Perhaps appellant's specific illustrative disclosure of an embodiment of his invention is limited to polymerizable materials "that are in fact *fiber-forming* polymers." However, that is no basis for a lack of enablement rejection. While appellant's pre-filtering invention undoubtedly is for the stated purpose of removing pigment agglomerates from fiber-

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forming polymers, appellant's statement of utility does not thereby mean that he is unable to claim his filtering process more broadly. The first paragraph of § 112 requires only that the specification enable any person skilled in the art to which the invention pertains to make and use the invention. There has been no contention by the Patent Office that any person skilled in the art, if he wanted to filter a polymer which was not fiber-forming, would have any trouble doing so. The only other possible basis in the first paragraph of § 112 is the description requirement, relied upon by the solicitor, and dealt with next.

The Description Requirement

[2] The solicitor's reliance on what this court has referred to as the "description requirement" of the first paragraph of § 112 is misplaced. The so-called "description requirement," which exists in the first paragraph independent of the enablement (how to make and how to use) portions, serves essentially two functions. In the simple case, where no prior application is relied upon, the description requirement is that the invention claimed be described in the specification as filed. In re DiLeone, 58 CCPA 925, 436 F.2d 1404, 168 USPQ 592 (1971); In re DiLeone, 58 CCPA 934, 436 F.2d 1033, 168 USPQ 598 (1971); In re Smythe, 480 F.2d 1376, 1385, 178 USPQ 279, 286 (CCPA 1973). As such, a rejection on the description requirement is tantamount to a new matter rejection under 35 U.S.C. 132. In re Smythe, supra. Both are fully defeated by a specification which describes the invention in the same terms as the claims. Here there has been no assertion by the board or the examiner that there is any lack of correspondence between the appealed claims and the specification (including the original claims) as filed. Indeed the scope of the language of the specification clearly corresponds to the language of the claims, the "polymerizable material" of the claims being referred to variously by the specification as a "polymer" and a " *polymerizable* mass * * * added * * * as an aqueous solution of monomeric *material,* such as hexamethylenediamine adipate." (Emphasis supplied.) * Thus there is no basis for the solicitor's reliance upon the description requirement as support for the rejection here.

Summary

The rejection of claims 1 and 3-11 under § 112, paragraph one, is *reversed.*

Footnotes

Footnote * In another situation where the "description requirement" is relied upon, namely, where the benefit of a prior application is being claimed under 35 U.S.C. 120, the description requirement comes into play as mandating a description of the invention, which is claimed in the later-filed case, in the specification of the application relied upon for support under the statute. See In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971).

- End of Case -

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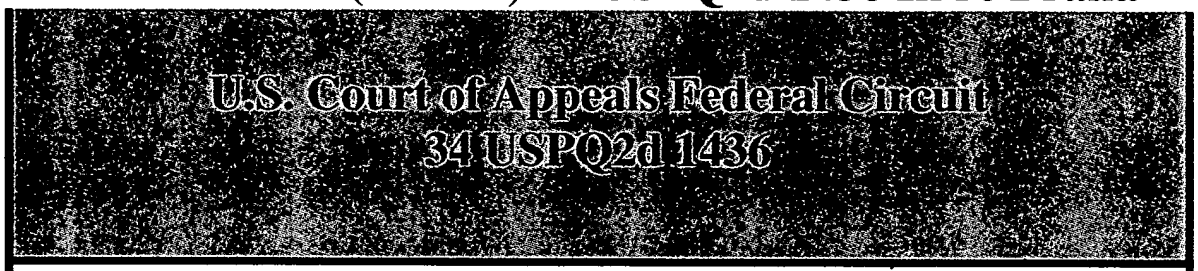

Decided March 30, 1995
No. 93-1393

Headnotes

PATENTS

1. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific lymphocytic tumors.

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2. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal. Reversed.

Attorneys:

Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

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Judge:

Before Plager, Lourie, and Rader, circuit judges.

Opinion Text

Opinion By:

Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). 1 The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) 2 directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:

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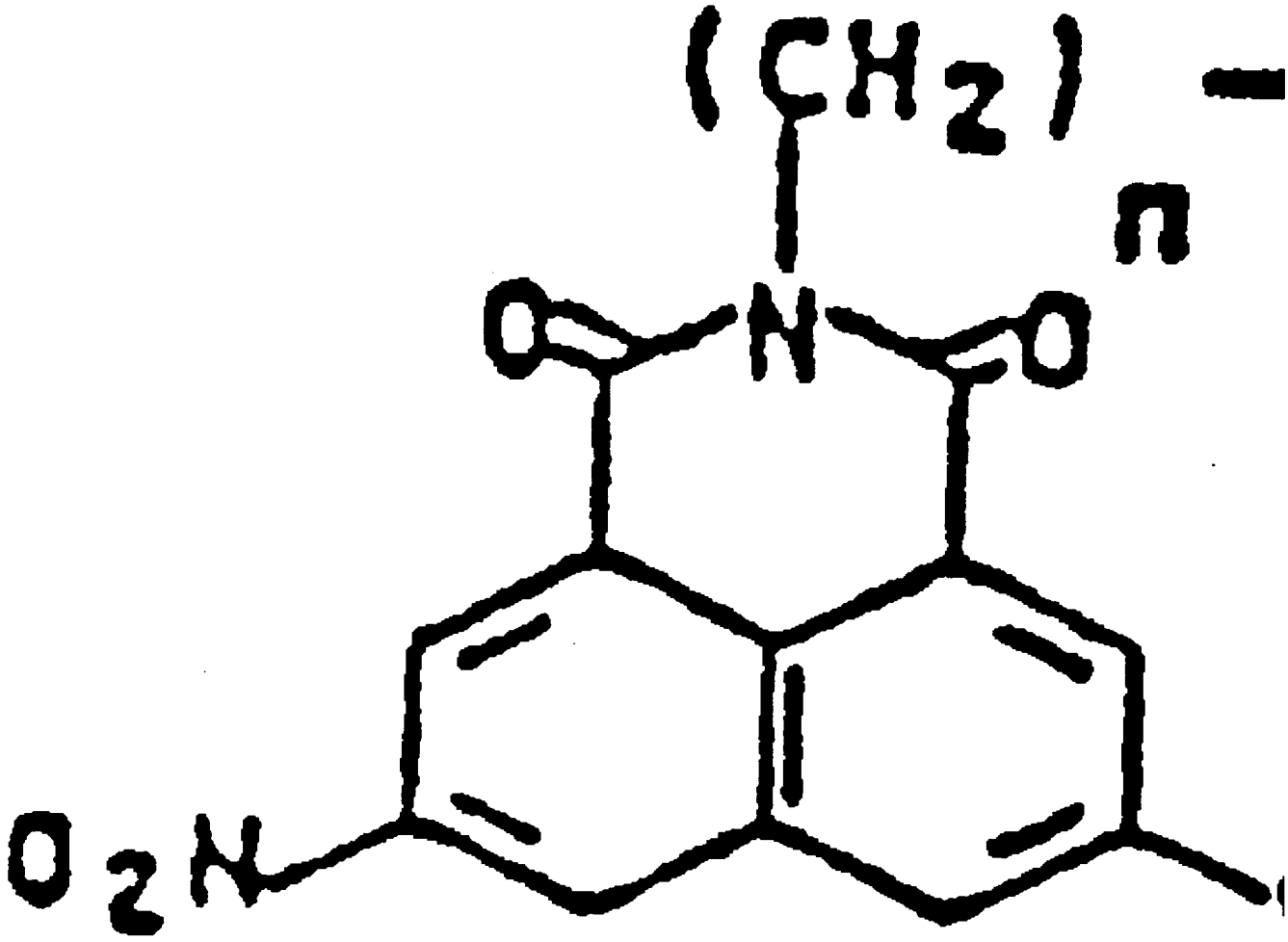

where n is 1 or 2, R [1] and R [2] are identical or different and are each hydrogen,

C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R [3] and R [4] are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR [3]R [4]) at the 8-position of the isoquinoline ring.

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The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* 3 against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. 4 These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* 5 and concludes that these tests "had a good action." 6

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. 7 Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. 8 Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action

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dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.
In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. 9 The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). 10
In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board affirmed solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 11 We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed. Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).
The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.
As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. 12 The Board gives two reasons for the rejection; 13 we will consider these in turn.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

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claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the

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effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, 15 the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. 16

This court's predecessor has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). 17

[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, 18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

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Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F.2d at 224, 169 USPQ at 370.

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration 19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

model *in vivo.* Such evidence alone should have been sufficient to satisfy applicants' burden.

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F.2d at 891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F.2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. 20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard

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experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed. Cir. 1994) (in banc), *In re Caveney,* 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed. Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952

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F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *In re De Blauwe,* 736 F.2d 699, 222 USPQ 191 (Fed. Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F.3d 1560, 1565 (Fed. Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. 21

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

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the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is reversed. *REVERSED* .

Footnotes

Footnote 1. Unless otherwise noted, all United States Code citations are to the 1988 edition.

Footnote 2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.

Footnote 3. *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

Footnote 4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

Footnote 5. *See supra* note 3.

Footnote 6. The specification does not state the specific type of human tumor cells used in this test.

Footnote 7. The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro

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groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

Footnote 8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

Footnote 9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.

Footnote 10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

Footnote 11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).

Footnote 12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112 Para.1.

Footnote 13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

Footnote 14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

Footnote 15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).

Footnote 16. As noted, this would appear to be a Section 101 issue, rather than Section 112.

Footnote 17. *See also In re Novak,* 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted

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scientific principles.").
Footnote 18. *See supra* note 15.
Footnote 19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).
Footnote 20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.
Footnote 21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

- End of Case -

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In re Bundy

(CCPA)
209 USPQ 48
Decided Feb. 26, 1981
No. 80-591
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Patentability -- Utility (§ 51.75)

Pleading and practice in courts -- Burden of proof -- In general (§ 53.131)

Pleading and practice in Patent Office -- Rejections (§ 54.7)

Specification -- Sufficiency of disclosure (§ 62.7)

Burden shifts to appellant to provide rebuttal evidence, where enablement question is whether disclosure of utility in terms of being useful and used in same manner as known series of analogs of prostaglandins is sufficient to satisfy how-to-use requirement of first paragraph of 35 U.S.C. 112, only when Patent Office has adequate support for its challenge to credibility of applicant's statements as to utility.

2. Specification -- Sufficiency of disclosure (§ 62.7)

Disclosure of some activity coupled with knowledge as to use of this activity is necessary to satisfy how-to-use requirement of Section 112.

3. Specification -- Sufficiency of disclosure (§ 62.7)

Situation in which sufficient guidelines as to use are given in disclosure is not same situation as in In re Gardner, 166 USPQ 138; no parallel can be drawn to In re Kirk, 153 USPQ 48, where in present case basic pharmacological activity has been established and not merely presumed from similar molecular structure.

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4. Patent grant -- Intent of patent laws (§ 50.15)

Specification -- Sufficiency of disclosure (§ 62.7)

Early filing of application with its disclosure of novel compounds that possess significant therapeutic use is to be encouraged; requiring specific testing of thousands of prostaglandin analogs encompassed by claim in order to satisfy how-to-use requirement of Section 112 would delay disclosure and frustrate, rather than further, interests of public.

5. Pleading and practice in Patent Office -- Rejections (§ 54.7)

Specification -- Sufficiency of disclosure (§ 62.7)

Although holding that appellant has adequately told how to use novel compounds necessarily undercuts best mode rejection founded on lack of enablement, thrust of inquiry is not same for determining satisfaction of further requirement that specification set forth best mode contemplated by inventor for carrying out his invention; satisfaction of best mode requirement of Section 112 is question separate and distinct from question of sufficiency of disclosure to comply with enablement provision; question is one of concealment, i.e., whether applicant has withheld what he considers to be best mode of carrying out his invention; best mode requirement does not require one to obtain further knowledge but only to disclose what one knows or, at least, contemplates.

6. Specification -- Sufficiency of disclosure (§ 62.7)

Inference of withholding of information as to best mode of use cannot be made from appellant's general statements of increased selectivity and narrower spectrum of potency of novel analogs that are conclusions that could be drawn from elementary pharmacological testing of prostaglandin analogs that established basic E-type activity.

Particular patents -- Prostaglandins

Bundy, 3,7-Inter-m-Phenylene-4,5,6-Trinor-2-Decarboxy-2-Hydroxymethyl-9 - Deoxy-9-Methylene-PGF-Type Compounds, rejection of sole claim reversed.

Case History and Disposition:

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of Gordon L. Bundy, Serial No. 832,329, filed Sept. 12, 1977, division of application, Serial No. 682,848, filed May 4,

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1976, issued as U.S. patent No. 4,060,530, Nov. 29, 1977. From rejection of sole claim, applicant appeals. Reversed.

Attorneys:

Robert A. Armitage, Kalamazoo, Mich., for appellant.

Joseph F. Nakamura (Gerald H. Bjorge, of counsel) for Patent and Trademark Office.

Judge:

Before Markey, Chief Judge, and Rich, Baldwin, Miller, and Nies, Associate Judges.

Opinion Text

Opinion By:

Nies, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of the sole claim of appellant's application [1] under the first paragraph of 35 USC 112. [2] We reverse.

The appeal raises questions regarding the extent to which new pharmaceuticals must be tested, preceding the filing of an application, in order to satisfy the how-to-use and best mode requirements of §112.

The Invention

The invention relates to a new series of analogs of naturally-occurring prostaglandins [3] which differ from the corresponding known prostaglandins in that these analogs have a methylene group at the C-9 position [4] . Structurally, the compounds may be considered analogs of either E-type prostaglandins (PGEs) in which the methylene group replaces the usual C-9 keto- or oxo-group or of F-type prostaglandins (PGFs) in which the methylene group replaces the C-9 hydroxyl group. Pharmacologically, however, the analogs are related only to PGEs.

The sole claim reads:

131. A prostaglandin analog of the formula

Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

wherein Y $_1$is trans --CH=CH--, --C=C--, or --CH $_2$CH $_2$;

wherein M $_1$is

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or
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wherein R_5 is hydrogen or methyl;

wherein L_1 is
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or a mixture of
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and
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wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

wherein g is one, 2 or 3; and
wherein m is one to 5, inclusive.

The Disclosure

The specification of U.S. Patent No. 4,060,534 ('534) has been incorporated by reference to serve as the specification for the present application. The portions of the specification directed to using these novel analogs are pertinent to the issues on appeal.

The background section of the specification contains a detailed description of the uses of various *known* PGE_S. Nine specific biological responses caused by PGE_S, ranging from decreasing blood pressure to inhibiting gastric secretion, are listed. Based on these responses, various pharmacological uses with broad ranges of dosage by various methods of administration are enumerated.

The use of appellant's novel analogs, which include not only the claimed compounds of this application, but also those claimed in other divisional applications and in '534, is subsequently set forth:

> The novel prostaglandin analogs of this invention correspond to the prostaglandins described above in that the novel prostaglandin analogs exhibit prostaglandin-like activity.

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Specifically the 9-deoxy-9-methylene-PGF-type compounds of this invention correspond to the PGE compounds described above, in that these novel 9-deoxy-9-methylene-PGF-type compounds are useful for each of the above-described purposes for which the PGE compounds are used, and are used in the same manner as the PGE compounds, as described above.

The PGE compounds described above, are all potent in causing multiple biological responses even at low doses. Moreover, for many applications, these prostaglandins have an inconveniently short duration of biological activity. In striking contrast, the novel prostaglandin analogs of this invention are substantially more selective with regard to potency in causing prostaglandin-like biological responses, and have a substantially longer duration of biological activity. Accordingly, each of these novel prostaglandin analogs is surprisingly and unexpectedly more useful than one of the corresponding prostaglandins described above for at least one of the pharmacological purposes indicated above for the latter, because it has a different and narrower spectrum of biological potency than the known prostaglandin, and therefore is more specific in its activity and causes smaller and fewer undesired side effects than when the prostaglandin is used for the same purpose. Moreover, because of its prolonged activity, fewer and smaller doses of the novel prostaglandin analog are frequently effective in attaining the desired result.

The specification includes a disclosure relating to preparation of the compounds generally, and several specific examples. None, however, are compounds within the subgenus claimed in this application.

No example of a specific use of *any* of the disclosed prostaglandin analogs, i.e., setting forth a dosage to achieve a desired response, is given.

The Rejection

The examiner rejected the sole claim under the first paragraph of 35 USC 112 as being "inadequately supported by the instant specification" in that not a single example was directed to one of the claimed compounds. Failure to meet the best mode requirement was also raised on the basis of no exemplification. Reliance on utilities similar to known PGE $_S$was attacked on the basis of a statement in a "Samuelsson et al. reference" (more correctly, a Rosenthale paper therein) [5] that "small changes in the [prostaglandin] molecule can alter potency or even induce diametrically opposite pharmacologic effects." Thus, the utilities asserted on the basis of those known for structurally analogous compounds were said to be "at best highly speculative."

Before the board the §112 rejection was more specifically explained by the examiner to encompass an inadequate disclosure of: (1) the description of the compounds; (2) the preparation of the same; (3) their use; and (4) the best mode of carrying out the invention. The examiner added that an undue amount of experimentation would be required to prepare the claimed compounds and to determine their utilities.

The board held that the description and how-to-make requirements of the first paragraph of 35 USC 112 were satisfied by appellant's disclosure. It agreed with the examiner, however, that:

[U]ndue experimentation would be required on the part of one of ordinary skill in

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> the relevant art to determine how to use the compounds claimed. Since we consider the manner of using a compound to be necessarily a part of "the best mode contemplated by the inventor of carrying out the invention", we also agree with the examiner's position that the best mode requirement has not been met.

The challenge raised by the examiner's citation of the Rosenthale paper was deemed reasonable and unrebutted by any factual evidence. The board then added:

> [O]ne of the advantages alleged for the compounds here claimed is that they are more selective than the analogous PGE compounds. This is an express indication

> that not all of the compounds covered by appellant's claims will induce the same biological responses.

Accordingly, the board affirmed the examiner's rejection of the sole claim to the extent it was based on the how-to-use and best mode requirements of §112.

Opinion

How-to-Use

. The enablement question present here is whether the disclosure of utility in terms of being useful and used in the same manner as known PGEs is sufficient to satisfy the how-to-use requirement of the first paragraph of 35 USC 112.

[1] The PTO must have adequate support for its challenge to the credibility of applicant's statements as to utility. Only then does the burden shift to appellant to provide rebuttal evidence. In re Gardner, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973); In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367 (1971). We must consider the Rosenthale paper in its entirety in determining the reasonableness of the doubt raised by the authors' conclusory statement relied on by the examiner, and in so doing see no specific evidence that structural variations of PGEs cause opposite pharmacologic effects. The tests reported by Rosenthale do indicate shifts in PGF $_{2a}$activity from bronchoconstrictor to broncodilator concomitant with structural changes. For PGE Rosenthale shows only variations in potency, a matter of degree of activity. Accordingly, we do not agree that Rosenthale is sufficient support for the examiner's position that the subject analogs, related as they are to PGE $_{s}$in pharmacological activity, may not be useful at all to achieve a particular response.

The board focused on another reason for challenging the disclosure as non-enabling. Appellant's disclosure of increased "selectivity" of the novel analogs was taken as an express indication that it was uncertain "which compound will induce which biological responses * * *," thus virtually ensuring that an undue amount of experimentation would be required to use the invention. The ranges of dosage for known PGEs, assuming their applicability to appellant's analogs, were said to be very broad and would, in any event, provide little guidance in determining dosages for the more selectively functional claimed analogs.

Appellant contends that the disclosure teaches that *all* novel compounds exhibit *each* of the enumerated pharmacological uses. The increased selectivity is said to be with respect to the potency for each activity, not to the existence of that biological activity.

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Any contrary interpretation of the specification is strongly denied. As far as determining dosages for the novel analogs is concerned, it is urged that the experimentation needed to ascertain proper levels for various responses would not be undue, but rather would lie well within the ability of one of ordinary skill in the art. At most, appellant states, the question is whether the determinations would be extended, not undue.

[2] We have no difficulty with appellant's interpretation of "selectivity". In the pertinent section, previously quoted, it is clearly stated that the novel compounds are "useful for *each* of the above-described purposes for which the PGE compounds are used" (emphasis added). This can only reasonably be read as teaching that *each* compound can be used for *each* and every one of the aforesaid biological responses. Appellant's further statements that the novel analogs are "substantially more selective with regard to potency" or "more specific in its activity" because of a "different and narrower spectrum of biological potency," does not negate the asserted usefulness for each purpose. There is no requirement that all have the same degree of activity for each use. What is necessary to satisfy the how-to-use requirement of §112 is the disclosure of some activity coupled with knowledge as to the use of this activity. In re Gardner, 475 F.2d at 1392, 177 USPQ at 398.

Thus the remaining question is whether appellant's disclosure is sufficient to enable one of ordinary skill in the art to use these novel analogs. No specific examples of dosages for human use or even animal tests are given for the novel compounds per se. Appellant's counsel stated at oral argument that all that had been established at the time of filing the application was the basic pharmacology for these compounds. Appellant's specification discloses that these compounds possess activity similar to E-type prostaglandins. As to the latter, dosages are disclosed, albeit expressed in very broad ranges.

[3] We do not consider that one of ordinary skill in the art would not know how to use these novel analogs to determine the specific dosages for the various biological purposes. We are persuaded that sufficient guidelines as to use are given in the disclosure here. This is not the same situation as in In re Gardner et al., 57 CCPA 1207, 427 F.2d 786, 166 USPQ 138 (1970). Here

only the compounds themselves are being claimed, not their therapeutic use. Nor can a parallel be drawn to In re Kirk, 54 CCPA 1119, 376 F.2d 936, 153 USPQ 48 (1967), the basic pharmacological activity having been established in this case, not merely *presumed* from similar molecular structure.

[4] Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

Accordingly, we are satisfied that the how-to-use requirement of the first paragraph of §112 has been adequately complied with by appellant's disclosures.

Best Mode

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[5] Turning to the best mode issue, we agree with appellant that this rejection was founded on a lack of enablement by both the examiner and the board. Our holding that appellant has adequately told how to use the novel compounds necessarily undercuts this position. However, we do not agree that the thrust of the inquiry is the same for determining satisfaction of the further requirement that the specification shall set forth the best mode contemplated by the inventor of carrying out his invention.

Satisfaction of the best mode requirement of §112 is a question separate and distinct from the question of the sufficiency of the disclosure to comply with the enablement provision. In re Gay, 50 CCPA 725, 731, 309 F.2d 769, 772, 135 USPQ 311, 315 (1962). The question is one of concealment, i.e., whether an applicant has *withheld* what he considers to be the best mode of carrying out his invention. The best mode requirement does not require one to obtain further knowledge but only to disclose what one knows or, at least, contemplates.

The Solicitor argued that concealment may be inferred. Quoting the disclosure in the specification that each analog is "surprisingly and unexpectedly more useful than one of the corresponding prostaglandins * * * for at least one of the pharmacological purposes * * *," he urges that appellant must have had test results to substantiate this statement and this data should have been disclosed. The alleged withholding of information on which these general statements were made is said to render the quality of disclosure so poor that it effectively results in concealment, citing In re Sherwood, 613 F.2d 809, 816, 204 USPQ 537, 544 (CCPA 1980).

[6] Were we to see merit in the Solicitor's position fairness would require providing appellant with the opportunity to present evidence in rebuttal. However, we do not find it necessary for appellant to assume this burden of proof. We can infer no withholding of information as to the best mode of use from appellant's general statements of increased selectivity and narrower spectrum of potency for these novel analogs, conclusions which could be drawn from the elementary pharmacological testing of the analogs which established the basic E-type activity.

Accordingly, we reverse the holding that the best mode requirement has not been satisfied.

Conclusion

The board's affirmance of the rejection of appellant's sole claim under both the how-to-use and the best mode requirements of the first paragraph of §112 is *reversed.*

Reversed.

Footnotes

Footnote 1. Serial No. 832,329, filed September 12 1977, for 3, 7-Inter-m-Phenylene-4, 5, 6-Trinor-2-Decarboxy-2-Hydroxymethyl- 9 -Deoxy-9-Methylene-PGF-Type Compounds. The application is a divisional application of Ser. No. 682,848, filed May 4, 1976, issued as U.S. Patent No. 4,060,534 on November 29, 1977.

Footnote 2.

The first paragraph of §112 reads:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and

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exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Footnote 3. Natural prostaglandins are found in mammalian tissues and have varied pharmacologic uses including the treatment of hypertension, ulcers and asthma, and the interruption of pregnancy. In naming the prostaglandins, the prefix PG is followed by a letter designating the oxidation state of the cyclopentane ring; thus arise the series PGA, PGE, PGF, etc. The numeral subscript refers to the number of double bonds in the side chain. 1 D. Lednicer & L. Mitscher, The Organic Chemistry of Drug Synthesis, 23-27 (1977).

Footnote 4. A typical example of a naturally-occurring prostaglandin is PGE_2 which structurally is represented:

Graphic material consisting of a chemical formula or diagram set at this point is not available. See text in hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.

Footnote 5. Cited by the examiner as: Samuelsson et al., Advances in Prostaglandin and Thromboxane Research, Vol. 1 (1976) 488-491.

Appellant has pointed out that the work relied upon is a paper by Rosenthale et al. entitled "Actions of Prostaglandins on the Respiratory Tract of Animals," pp. 477-493 included in the above book, edited by Samuelsson et al. Henceforth we shall refer to this reference as the Rosenthale paper.

- End of Case -

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Characterization of Polymer Miscibility by Fluorescence Techniques. Blends of Styrene Copolymers Carrying Hydrogen Bond Donors with Polymethacrylates[1]

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ABSTRACT: A styrene copolymer with a small proportion of *N*-carbazolylethyl methacrylate (CEM) and styrene terpolymers with CEM and methacrylic acid (MA), methacryloyl glycine (MAG), styrenesulfonic acid (SSA), *p*-(hexafluoro-2-hydroxylisopropyl)styrene (HHIS), or *p*-vinylphenol (VP) were prepared. Films of these polymers blended with copolymers of methyl methacrylate, ethyl methacrylate, or butyl methacrylate with 9-anthrylmethyl methacrylate (AMM) were cast from toluene, dioxane, or chloroform solution and the intimacy of the mixing of the components of these blends was characterized by nonradiative energy transfer (NET) from the carbazole to the anthracene fluorophore. The miscibility of the polymers depended strongly on the casting solvent and was much better for styrene copolymers with HHIS or VP than for styrene copolymers with MA, MAG, or SSA. Stronger excimer emission was observed in polystyrene blends with poly(ethyl methacrylate) than in blends with poly(methyl methacrylate), although NET indicated a better miscibility with poly(ethyl methacrylate); this was interpreted as due to the lesser rigidity of poly(ethyl methacrylate).

Introduction

Many years ago, Gee[2] pointed out that the mixing of long-chain molecules leads to a negligible entropy change, so that the mixture can be stable only if the mixing process is exothermic. In the absence of specific interactions, the ΔH is usually positive[3] and this is the reason why most polymer pairs resist mixing, so that even dilute solutions containing two polymers in a common solvent form two phases.[4] In a previous study from this laboratory[5] it was shown that such phase separation in solutions containing polystyrene (PS) and poly(methyl methacrylate) (PMMA) can be avoided if a small concentration of vinylpyridine is incorporated into the PS and if the PMMA is modified by a small concentration of methacrylic acid residues, so that the exothermic acid–base interaction overwhelms the unfavorable enthalpy characterizing the mixing of PS with PMMA. Later studies of polymer blends in bulk, carried out in many laboratories, demonstrated that a variety of immiscible polymers can be rendered compatible by utilizing the interactions of small numbers of acid and base,[6] ion pair and dipole,[7] hydrogen bond donor and acceptor,[8] or electron donor and acceptor[9] substituents.

In the mixing of polymer pairs for which the driving force for phase separation is relatively small, "fuzzy" phase boundaries are obtained, since the chains of each polymer penetrate some distance into the region in which the other polymer is the main component. The phase boundaries will gradually sharpen as the mixing of the polymers becomes more unfavorable[27] and the size of the phase domains will increase with an increasing interfacial energy. Different experimental techniques for the characterization of polymer miscibility may lead to different conclusions, since each technique will require some minimum size of phase domains to detect phase separation. Thus, Albert et al.[10] found that nonradiative energy transfer between fluorescent labels attached to poly(vinyl chloride) and syndiotactic PMMA decreased gradually with an increasing PMMA content in the blend, indicating some separation of the two polymers, although an earlier study[11] had reported a single T_g for blends containing up to 80 wt % PMMA. More recently, Shah[8c] reported that the introduction of acidic groups into polyacrylates renders their blends with poly(*N*-vinylpyrrolidone) optically transparent, because of the hydrogen bonding of the two polymers, while microphase separation is still demonstrated by electron microscopy.

In this report we describe results obtained on blending styrene copolymers containing various hydrogen bond donor residues (as shown in Figure 1) with polymers of methyl, ethyl, and butyl methacrylate (PMMA, PEMA, and PBMA) where the carbonyl group acts as a hydrogen bond acceptor. Two fluorescence techniques were used to characterize the compatibility of the blends.

(a) When the polymethacrylates were labeled with anthracene and the styrene copolymers with carbazole, the overlap between the carbazole emission and anthracene absorption spectra led to nonradiative energy transfer (NET)[12] so that on irradiation of a sample in the carbazole absorption band the ratio of carbazole and anthracene emission intensity, I_C/I_A, decreased with an increasingly intimate mixing of the two polymers.[13] The efficiency of NET is given by

$$\text{eff} = [1 + (r/R_0)^6]^{-1} \quad (1)$$

where r is the distance between the donor and acceptor fluorophore and the characteristic transfer distance R_0 has been determined to be 2.8 nm for the carbazole–anthracene pair.[13] The technique should be sensitive to phase separation involving phase domains exceeding this dimension.[28]

(b) In a homogeneous blend of PS with a nonfluorescing polymer, excimer emission has been shown[14] to increase relatively slowly with the PS concentration, indicating that excimer formation is predominantly intramolecular, requiring a statistically improbable conformation between two consecutive monomer residues in the ground state. On the other hand, PS in bulk exhibits only excimer emission, since phenyl residues attached to different chains can interact to form the excimer. This contrasting behavior can be exploited to characterize phase separation in polystyrene blends, as demonstrated by Gelles and Frank.[14] We have tried to determine whether the ratio of the emission intensities of the excimer and the monomer band, I_e/I_m, of PS can also be used as a measure of polymer miscibility in our systems.

Experimental Section

Materials. 9-Anthrylmethyl methacrylate (AMM) and 2-(*N*-carbazolyl)ethyl methacrylate (CEM) were synthesized as previously described.[13] Methacryloyl glycine (MAG) was prepared from glycine and methacryloyl chloride in the presence of sodium hydroxide and phenothiazine polymerization inhibitor and *p*-(hexafluoro-2-hydroxylisopropyl)styrene (HHIS) was synthesized by the method of Pearce et al.[8a] *p*-Acetoxystyrene (AS) from Allied

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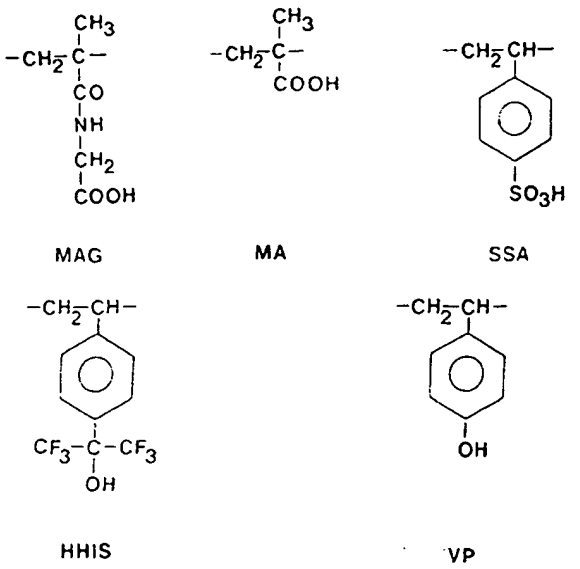

Figure 1. Styrene comonomers used as hydrogen bond donors.

Chemical Co. was vacuum distilled before use. Sodium styrene sulfonate was purchased from Polysciences Inc.

Polymers. Polymerizations were carried to low conversion at 60 °C in dioxane solution (except for the terpolymers containing sodium styrene sulfonate, for which a dioxane mixture with methanol was used) with ABIN as initiator. Sodium styrenesulfonate terpolymers were converted to the acid form by passing HCl gas through the solution and filtering off the NaCl. Styrene terpolymers with AS were converted to the *p*-vinylphenol terpolymers in a mixture of dioxane and hydrazine hydrate, storing the solution for 4–5 h at room temperature. A dioxane solution of HCl was added to the product and the terpolymer was purified by several redissolutions in dioxane and precipitations into a large excess of methanolic HCl. The CEM and AMM contents of fluorophore-labeled polymers were determined by UV spectroscopy as previously described.[13] The content of carboxyl and sulfonic acid groups in styrene terpolymers was determined by titration with sodium methoxide in a 4:1 mixture of benzene and methanol with phenolphthalein as end point indicator. The content of AS residues in their terpolymers was determined in chloroform solution from the intensity of the carbonyl 1740 cm^{-1} IR band (allowing for the contribution from the CEM residues) by using poly(*p*-acetoxystyrene) as a standard. The data were consistent with the reactivity ratios for the copolymerization of styrene with AS as reported by Arshady et al.[15] The conversion of AS residues into vinyl phenol VP residues was followed by the disappearance of the carbonyl IR band. The composition of the HHIS terpolymer was obtained from the fluorine content by elemental analysis. The compositions and intrinsic viscosities of the labeled polymers are listed in Table I. The unlabeled polystyrene, poly(methyl methacrylate), poly(ethyl methacrylate), and poly(butyl methacrylate) had intrinsic viscosities (in dioxane at 25 °C) of 0.76, 0.98, 0.42, and 0.41 dL/g, respectively.

Sample Preparation and Fluorimetry. Films were cast from 8% solutions containing equal weights of the two polymers in a blend, unless specified otherwise. After evaporation of the solvent, the films were dried for at least a week under vacuum and were stored under vacuum up to the time of fluorescence measurement. Reflection spectra were recorded on a Perkin-Elmer MPF-44B fluorimeter using an excitation wavelength of 296 nm for blends of CEM and AMM labeled polymers. Energy transfer was characterized by I_C/I_A, the ratio of the carbazole emission intensity at 365 nm and the anthracene emission intensity at 413 nm. For unlabeled blends of polystyrene with polymethacrylates, excitation at 260 nm was used and the ratio I_e/I_m, of excimer emission at 340 nm and monomer emission at 285 nm, was recorded as a function of the composition of the blend.

DSC measurements were carried out by using a Du Pont Model 9900 DSC instrument. After heating at a rate of 10 °C/min up to 140 °C, the sample was quenched and the thermal behavior was recorded from 0 to 140 °C under nitrogen.

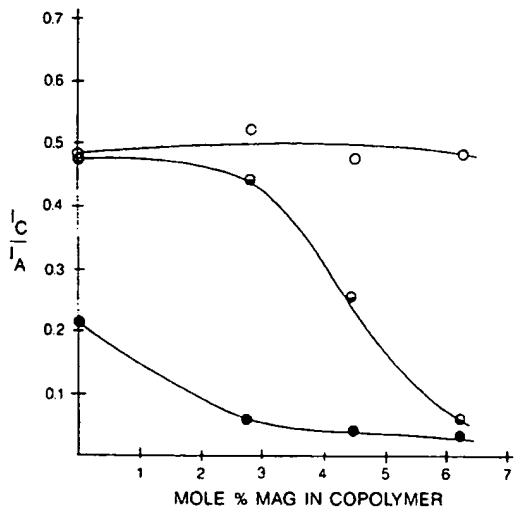

Figure 2. Ratio of donor and acceptor fluorescence in blends of PEMA with S–MAG. Films cast from chloroform (○), dioxane (◒), and toluene (●).

Table I
Characterization of Fluorophore-Labeled Polymers

polymer	mol % H bonding comonomer	mol % CEM	mol % AMM	$[\eta]$, dL/g, dioxane, 25 °C
PS		0.46		0.56
S-MA	3.3	0.45		0.43
S-MA	3.9	0.48		0.45
S-MA	5.4	0.48		0.45
S-MA	6.6	0.47		0.52
S-MAG	2.8	0.50		0.44
S-MAG	4.4	0.51		0.43
S-MAG	6.2	0.52		0.43
S-SSA	1.2	0.48		0.25
S-SSA	1.9	0.51		0.21
S-SSA	2.8	0.51		0.17
S-HHIS	0.9	0.51		0.38
S-HHIS	1.4	0.51		0.36
S-HHIS	2.3	0.53		0.38
S-HHIS	4.6	0.53		0.39
S-HHIS	6.2	0.48		0.45
S-VP	0.94	0.50		0.39
S-VP	1.9	0.53		0.40
S-VP	3.8	0.51		0.43
S-VP	4.9	0.53		0.45
PMMA			0.49	0.66
PEMA			0.44	1.27
PBMA			0.51	1.11

Results and Discussion

Nonradiative Energy Transfer. For all the blends used in this study, the NET characterized by I_C/I_A depended on the solvent from which the film was cast. This feature is illustrated in Figure 2 for blends styrene–methacrylylglycine copolymers with poly(ethyl methacrylate). Compatibility is optimized by casting from toluene solutions; more segregation of the components of the blend was observed for films cast from dioxane which competes with PEMA as a hydrogen bond acceptor. For blends cast from chloroform, no improvement of compatibility was found when MAG residues were introduced into PS, presumably because the solvent supplanted completely the MAG as a hydrogen bond donor. It should be noted, however, that the dependence of compatibility on the casting solvent is also observed for the blend of the PS and PEMA homopolymers, where no hydrogen bonding is involved. It has been observed in various systems that the same polymer blend may lead to homogeneous or phase-separated films, depending on the solvent from which the film is cast[16] as would be generally expected if the solvent interacts much

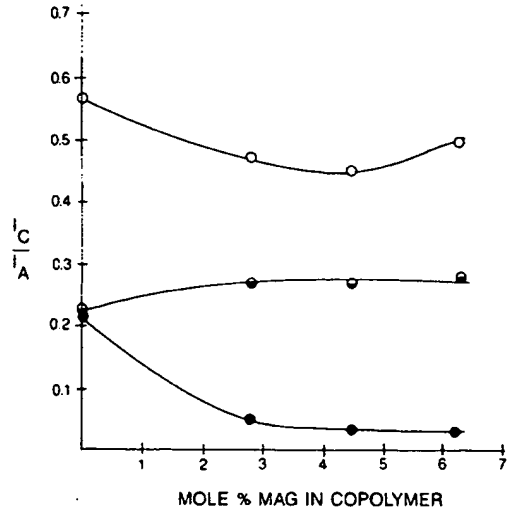

Figure 3. Ratio of donor and acceptor fluorescence in blends of S–MAG with PBMA (○), PMMA (⊖), and PEMA (●). Films cast from toluene.

more strongly with one component of the polymer pair.[17] If we use the difference between the Hildebrand solubility parameters[18] of the polymer, δ_p, and the solvent, δ_s, as a measure of polymer solvation, we find that with $\delta_p = 8.99$ for PEMA, $\delta_p = 9.04$ for PS,[19] $\delta_s = 8.9$ for toluene, and $\delta_s = 10.0$ for dioxane,[18] the $\delta_p - \delta_s$ are very similar for the two polymers in both casting solvents, so that no phase separation would be expected on the basis of a preferential solvation of one of the components of the blend. It seems then that a better mixing on the segmental level is brought about when casting the polymer blend from a strongly solvating medium (i.e., from toluene, characterized by a small value of $\delta_p - \delta_s$). On the other hand, if we compare blends of PS and styrene copolymers with different polymethacrylates, then the extent of phase separation is clearly correlated with $\Delta\delta_p$, the difference in the solubility parameters of the two polymers. For PS blends with PMMA, PEMA, and PBMA the $\Delta\delta_p$ are[19] 0.26, 0.05, and 0.56 and the data in Figure 3 show that, as expected, the PS–PEMA is closest and the PS–PBMA furthest from compatibility.

We were particularly interested in the relative efficiency of various styrene comonomers functioning as hydrogen bond donors in promoting compatibility with polymethacrylates. The MAG residue would be expected to be much more acidic than a methacrylic acid (MA) residue,[20] and since its carboxyl group is further from the chain backbone, it should be more accessible to the hydrogen bond accepting carbonyls of the polymethacrylates. Yet, we found in most experiments little difference in the compatibility of S–MAG and S–MA copolymers with polymethacrylates. The relative effectiveness of carboxyl and sulfonic acid groups in promoting compatibility was found to depend both on the polymethacrylate with which the styrene copolymer was blended and on the solvent from which the blend was cast. In blends of styrene copolymers with PEMA, the sulfonic acid was less efficient for films cast from toluene, while it clearly promoted compatibility for films cast from chloroform, where the MAG and MA comonomers were completely ineffective (Figure 4). In blends with PBMA, the sulfonic acid was more effective in compatibilizing PS films cast from either solvent (Figure 5). Unfortunately, the data for styrene copolymers carrying carboxyl and sulfonic acid groups are not strictly comparable, because of the much shorter chain length of the S–SSA copolymers as indicated by the intrinsic viscosity values in Table I. This difference in molecular weight was due to the difference in polymerization conditions: It was difficult to find a solvent medium for mixtures of styrene and sodium styrene sulfonate, so that the S–SSA copolymers had to be prepared in much more dilute solution than the other styrene copolymers. We tried to avoid this difficulty by sulfonating the styrene–CEM copolymer, but this procedure led to a change in the spectroscopic properties of the fluorophore.

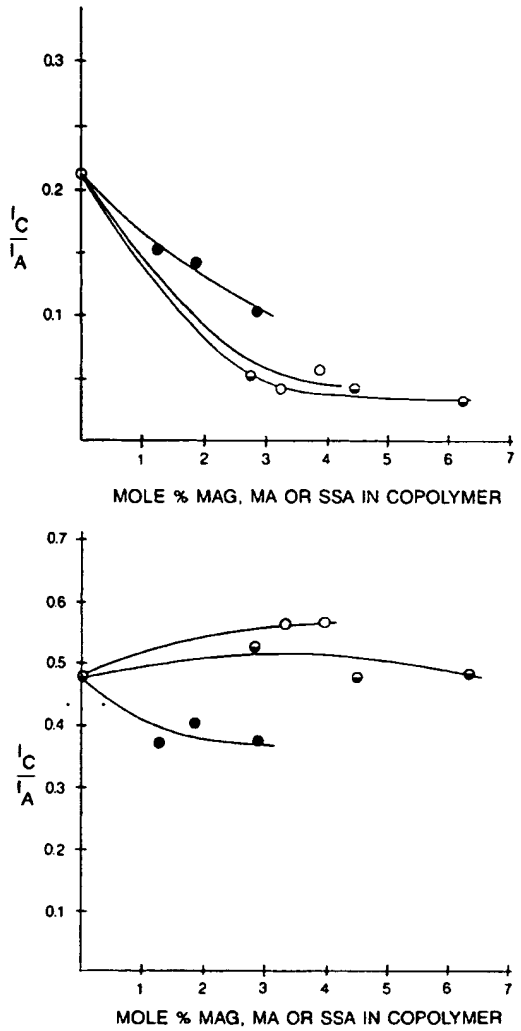

Figure 4. Ratio of donor and acceptor fluorescence in blends of PEMA with S–MA (○), S–MAG (⊖), and S–SSA (●). (Top) Cast from toluene; (bottom) cast from chloroform.

The HHIS fluorophore, first shown by Pearce et al.[8a] to be a powerful agent for rendering polystyrene compatible with polymers functioning as hydrogen bond acceptors, proved incomparably more efficient than MA, MAG, and SSA comonomers. This can be seen in comparing Figures 2 and 6—it is particularly striking that blends of S–HHIS with PEMA achieve a high degree of compatibility even when cast from chloroform. The degree of mixing on the segmental level which leads to optically clear films was obtained when the NET was characterized by $I_C/I_A < 0.1$; this was observed in films cast from toluene solutions for blends of PEMA or PBMA with a styrene copolymer containing as little as 0.9 mol % 0f HHIS residues.

The incorporation of VP residues into styrene copolymers was also found to be very effective in promoting compatibility with polymethacrylates. This is illustrated in Figure 7 for blends of S–VP copolymers with the three polymethacrylates cast from toluene and in Figure 8, which

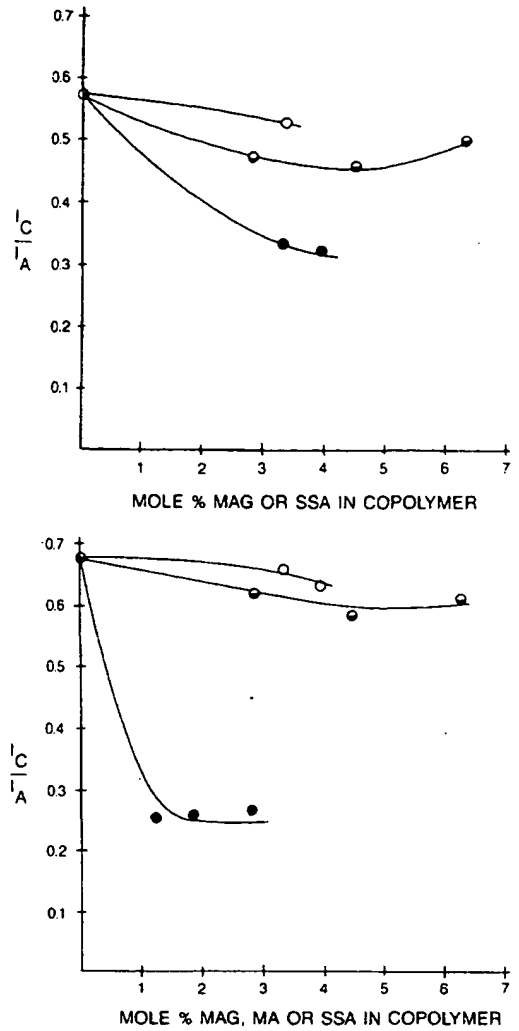

Figure 5. Ratio of donor and acceptor fluorescence in blends of PBMA with S–MA (○), S–MAG (⊖), and S–SSA (●). (Top) Cast from toluene; (bottom) cast from chloroform.

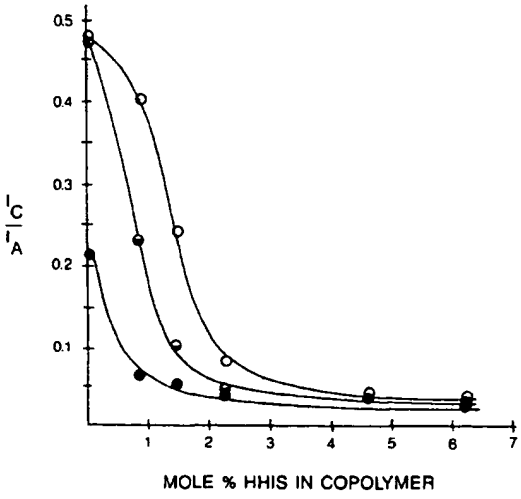

Figure 6. Ratio of donor and acceptor fluorescence in blends of PEMA with S–HHIS. Cast from dioxane (○); cast from chloroform (⊖); cast from toluene (●).

shows that whereas the acetoxy substituent has no effect on the compatibility of PS with PBMA, the efficiency of NET increases dramatically when the acetoxystyrene residues are converted to VP residues. However, our NET

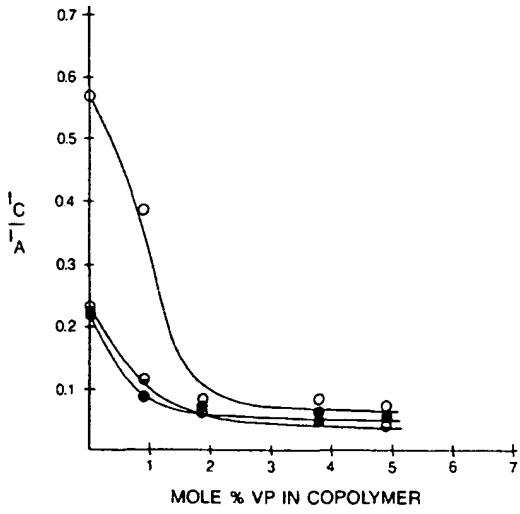

Figure 7. Ratio of donor and acceptor fluorescence in blends of S–VP with PBMA (○), PMMA (⊖), and PEMA (●). Films cast from toluene.

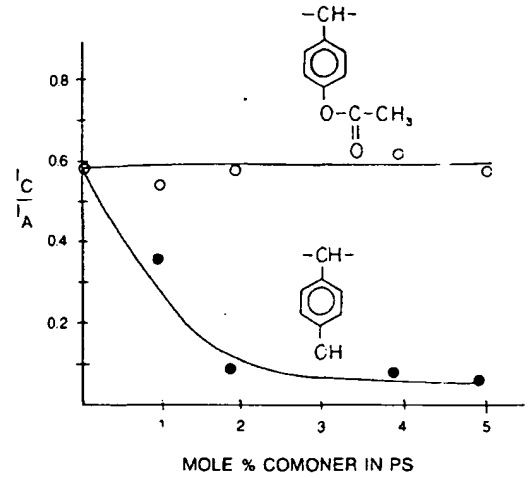

Figure 8. Ratio of donor and acceptor fluorescence in blends of PBMA with styrene copolymers with *p*-acetoxystyrene compared with this ratio after conversion of the *p*-acetoxystyrene to *p*-vinylphenol residues.

data showed that S–VP copolymers with a VP content above 70% are immiscible with PBMA. Here, the self-association of the phenolic residues dominates the hydroxyl–ester association.[24]

The interaction of VP residues with polymers acting as hydrogen bond acceptors was first studied by Moskala et al.[26] who used FT-IR spectroscopy to characterize hydrogen bonding in blends of the VP homopolymer with poly(vinyl acetate) and ethylene–vinyl acetate copolymers. Blends of poly(4-vinylpyridine) (PVPy) with S–VP copolymers were studied by de Meftahi and Frêchet,[21] who found that they required relatively high concentrations of VP residues to avoid phase separation (for instance, two T_g were observed in a blend of equal weights of PVPy and a styrene copolymer containing 30 mol % VP). These authors were apparently unaware of the effect of the casting solvent on the homogeneity of the film and since they cast their films from pyridine, a preferential solvation of the VP copolymer would be expected to have favored phase separation. In contrast with the results of de Meftahi and Frêchet, the fact that we found less than 1 mol % of VP residues in a S–VP copolymer to be sufficient to produce compatible films with PMMA and PEMA is striking. Only in blends with PBMA was the HHIS co-

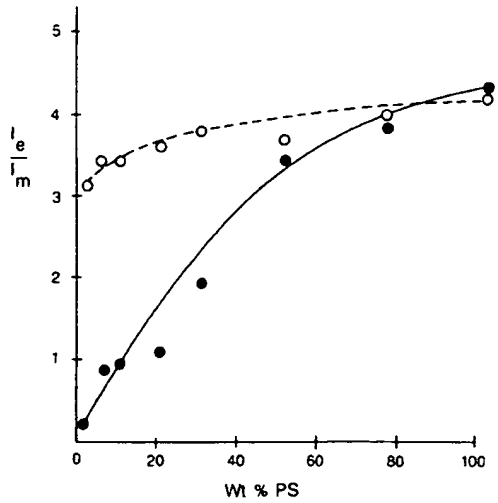

Figure 9. Ratio of excimer and monomer emission intensity in blends of PS with PMMA. Films cast from dioxane (○) and from toluene (●).

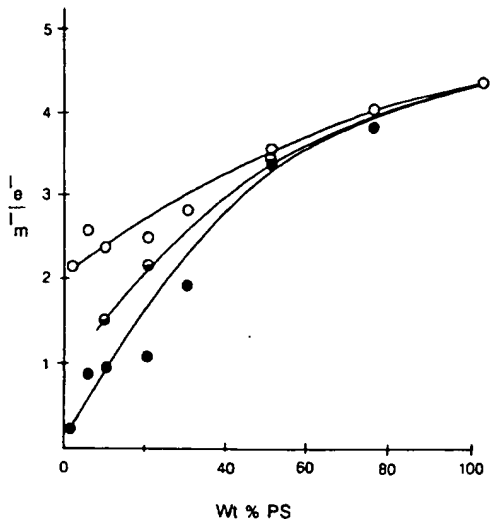

Figure 10. Ratio of excimer and monomer emission intensity in blends of PS with PBMA (○), PEMA (⊖), and PMMA (●). Films cast from toluene.

monomer more efficient than VP in promoting PS compatibility.

Excimer Emission. It has been shown by Gelles and Frank[14,22] that in blends of PS with poly(vinyl methyl ether) (PVME) the relative emission intensity of the excimer and the monomer, I_e/I_m, increases with the degree of phase separation. Two causes contribute to this effect: (a) Excitation energy migration becomes more efficient if it does not have to travel along the contour of the polymer chain but can hop from one polymer molecule to another. Thus, the probability that this excitation will reach a pair of monomer residues with a conformation favorable for excimer formation is enhanced. (b) As the concentration of PS in a phase increases, excimers may also be formed by the interaction of phenyl groups appended to different chains but placed in close proximity.

As expected, blends of PMMA containing moderate concentrations of PS are characterized by substantially higher I_e/I_m in films cast from dioxane than in films cast from toluene (Figure 9). This agrees with the result obtained by NET, which showed that toluene-cast films are more homogeneous. However, when we compared blends of PS with PMMA, PEMA, or PBMA cast from toluene (Figure 10), we found I_e/I_m to follow the order PBMA > PEMA > PMMA, although the NET data showed convincingly that PEMA is most compatible with PS (Figure 3). We believe that this discrepancy is due to the fact that PEMA is closer to its glass transition (T_g = 70 °C) than PMMA (T_g = 100 °C). Thus, the lower rigidity of the blends of PS with PEMA allows neighboring styrene residues somewhat more freedom to acquire the excimer conformation. We conclude that NET, which should not be sensitive to variations in polymer rigidity, is a more reliable measure of PS compatibility with other polymers than excimer emission. The I_e/I_m ratio is also unsuitable for the study of effects of hydrogen-bonding comonomers in increasing PS compatibility, since even low concentrations of these comonomers reduce substantially excimer emission.

Differential Scanning Calorimetry. The compatibility of PS with PMMA cannot be studied by the DSC method, since T_g is close to 100 °C for both these polymers. Even with blends of PEMA ($T_g \sim 70$ °C) with PS, the small value of ΔT_g renders the evaluation of the DSC traces difficult. Nevertheless, the effect of the casting solvent on the phase behavior could be demonstrated; for instance, a PEMA blend with S–MA containing 3.3 mol % of methacrylic acid residues exhibited a single glass transition, at 90 and 81 °C respectively, when cast from toluene or dioxane, but two glass transitions, at 70 and 102 °C, when cast from chloroform. In the case of blends of PBMA (T_g = 30 °C) with the S–MA, S–MAG, and S–SSA copolymers, all the blends yielded DSC traces indicating two glass transitions, i.e., phase separation. Even with the S–HHIS copolymers, a content of 4.2 mol % of the acidic comonomer was required before the blend exhibited a single T_g.

Concluding Remarks. A significant result of this study is the demonstration that the hydrogen bond donor efficiency is not determined by the acidity. Thus, the hexafluoroisopropyl alcohol group with a pK^{23} = 9 and the phenolic group with a similar acidity were found to aid the compatibility of PS with polymethacrylates much more than carboxyl groups. It is true that carboxyl is both a hydrogen bond donor and acceptor and that in its latter role it may compete, in principle, with the carbonyl groups of polymethacrylates,[24] but in view of the much larger concentration of ester groups in the systems which we have studied, it seems unlikely that this is a significant factor in explaining the relatively low efficiency of MA and MAG comonomers in promoting PS miscibility with polymethacrylates. In fact, the lack of correlation between the acidity and the efficiency of donating a hydrogen bond has a corollary in the absence of a correlation between hydrogen bond acceptance and the basicity, with dimethylacetamide being a more powerful hydrogen bond acceptor than pyridine.[25]

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Registry No. (CEM)(S) (copolymer), 116910-77-1; (CEM)(S)(MA) (copolymer), 116910-78-2; (CEM)(MAG)(S) (copolymer), 116910-79-3; (CEM)(HHIS)(S) (copolymer), 116910-80-6; (AMM)(MMA) (copolymer), 33773-67-0; (AMM)(EMA) (copolymer), 78949-80-1; (AMM)(BMA) (copolymer), 116910-83-9.

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(28) We have recently demonstrated (Horsky; Morawetz, H. *Macromolecules*, submitted for publication) that some of the energy transfer observed in blends of donor and acceptor labeled polymers is radiative, i.e., independent of the spacial distribution of the fluorescent labels. Thus, energy transfer data cannot be interpreted in terms of the dimensions of phase domains as suggested by Albert et al. in ref 10.

Fluorescence Study of the Complexation of Poly(acrylic acid) with Poly(*N*,*N*-dimethylacrylamide-*co*-acrylamide)

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ABSTRACT: Complex formation of poly(acrylic acid) (PAA) with the *N*,*N*-dimethylacrylamide (DAAm) homopolymer and its copolymers with acrylamide (AAm) in water solution was characterized by the enhancement of fluorescence of dansyl labels attached to the PAA. The complexation was more pronounced at pH 3 where the acrylamide residues seemed to contribute to complex stability, while at pH 4 no complex was formed with a copolymer containing 55 mol % AAm. The ratio of monomer residues in PAA and the copolymer in the complexes was independent of the copolymer composition. A number of arguments contradict the concept that polymer complexation in water solution by cooperative hydrogen bonding requires the interaction of long sequences of contiguous monomer residues.

Introduction

Many investigations have been reported on polymer complexation by cooperative hydrogen bonding.[1] If such complexation takes place in aqueous solution, there is only a small difference between the strength of the interpolymer hydrogen bond and the hydrogen bonds of the two polymers with water. It is then not surprising that a large number of interpolymer bonds must be formed to yield a stable complex. It has been claimed[1a] that such complexation involves "noninterrupted linear sequences of bonds" between monomer residues of the hydrogen bond donor and the hydrogen bond acceptor polymer, but it was pointed out that this would involve prohibitive steric strain.[2] It has also been shown that alternating copolymers of carboxylic acids with maleic anhydride form stable complexes with poly(*N*-vinylpyrrolidone) (PVP) in aqueous solution.[3]

Whereas the results obtained with alternating copolymers demonstrate that hydrogen-bonded polymer complexes may form in water solution even if the interacting groups are not attached to neighboring monomer residues, a study of the complexation of a homopolymer with a series of random copolymers containing varying concentrations of inert monomer residues should shed additional light on factors determining complex stability. Bimendina et al.[4] studied complexation of poly(methacrylic acid-*co*-methyl methacrylate) containing 63.6–76.8 mol % of the acid monomer residues with PVP, but this system could only be investigated in water containing 30% ethanol. Iliopoulos et al.[5] considered partially ionized poly(acrylic acid) (PAA) as a random copolymer of hydrogen-bonding and inert monomer residues and studied the complexation of PAA at varying degrees of ionization with poly(oxyethylene) or PVP.

Unfortunately, the introduction of a comonomer into one of the partners of complex forming polymers can never be considered a "structure defect"[5] only, since it will affect the complex stability in various other ways: This may involve hydrophobic interactions stabilizing the complex,[6,12] or in the case of partially ionized PAA, a strong interaction of the anionic acrylate residues with water, which would be expected to weaken the cohesion of the interacting polymer chains. To minimize this difficulty, we chose for our study the complex formation of PAA with

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in the claims, the limitation in and of itself may enable one skilled in the art to make and use the claim containing the limitation. When claimed subject matter is only presented in the claims and not in the specification portion of the application, the specification should be objected to for lacking the requisite support for the claimed subject matter using Form Paragraph 7.44. See MPEP § 2163.06. This is an objection to the specification only and enablement issues should be treated separately.

2164.01 Test of Enablement

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

UNDUE EXPERIMENTATION

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

2164.01(a) Undue Experimentation Factors

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

2164.04 Burden on the Examiner Under *>the< Enablement Requirement [R-1]

Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. See *Genentech v. Wellcome Foundation*, 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994).

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing *In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)) (discussed in MPEP § 2164.07 regarding the relationship of the enablement requirement to the utility requirement of 35 U.S.C. 101).

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact.

For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

In accordance with the principles of compact prosecution, if an enablement rejection is appropriate, the first Office action on the merits should present the best case with all the relevant reasons, issues, and evidence so that all such rejections can be withdrawn if applicant provides appropriate convincing arguments and/or evidence in rebuttal. Providing the best case in the first Office action will also allow the second Office action to be made final should applicant fail to provide appropriate convincing arguments and/or evidence. Citing new references and/or expanding arguments in a second Office action could prevent that Office action from being made final. The principles of compact prosecution also dictate that if an enablement rejection is appropriate and the examiner recognizes limitations that would render the claims enabled, the examiner should note such limitations to applicant as early in the prosecution as possible.

In other words, the examiner should always look for enabled, allowable subject matter and communicate to applicant what that subject matter is at the earliest point possible in the prosecution of the application.

2164.05 Determination of Enablement Based on Evidence as a Whole

Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art.

Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); *cf. In re Alton*, *76* F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered).

Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention. In chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). Once that evidence is submitted, it must be weighed with all other evidence according to the standards set forth above so as to reach a determination as to whether the disclosure enables the claimed invention.

To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be

Characterization Techniques for Polymer Blends

There are many techniques that are sensitive to the phase (size and / or structure) of the blends system. For example, thermal analysis and thermo mechanical analysis, which measure the T g of the blends. By using direct methods like Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), we can visualize the morphology and phase structure of the blends. There are also other techniques like Electron Spectroscopy for Chemical Analysis (ESCA), Small-angel Light Scattering (SAXS) and Small-angel Neutron Scattering (SANS) available for determine the compatibility of the blends from different aspects.

- **Cloudy point------** For a multiple-phase blends, the size of dispersed phase can vary from thousands of ångström to several tens of micrometer. The lower limit approaches the wavelength of visible light. So if the refractive index of the two phases differ quite a bit, the phase-separated blends will be turbid. But for micro-phase separated block copolymer, The domain size is less than few hundred ångström, still smaller than the wavelength of visible light. It is still optical clear. When phase structure of the blends changes with temperature, it is possible to use laser light scattering to determine the cloud points (phase boundary). It should be noticed here that this is not the thermodynamic phase diagram. Click here to see the chart comparing the refractive index for few polymers.

- **Glass transition temperature (T g)------- There can be one or multiple glass transitions for specific polymer blends. It has been used as one of the criteria for the miscibility of the two polymers. Differential Scanning Calorimetry (DSC), Dynamic Mechanical Analysis (DMA), Thermoelectrometry and Thermodilatometry are all suitable for this study. DSC and DMA are most commonly used. The following are examples of evidence of glass transitions in miscible and incompatible systems of polymer blends.**

- **Optical microscopy, Atomic Force Microscopy (AFM) and Electron Microscopy ------ With the development of imaging techniques, a direct observation of the phase structure (morphology, size and distribution) becomes possible. With an optical miscope, a phase with a size smaller than 0.2 μm can not be seen. So the electron microscopy is applied to observe phase domain of a size of 50-1000 ånström. This comes true with Transmission Electron Microscopy by applying dyeing techniques such as oxidizing the unsaturated domain with OsO_4 and RuO_4. SEM is generally for bigger domain observation, especially on the free or fractured surface. AFM is a relative new technique that will allow a direct visualization of surface morphology of polymers. Here is a link of AFM for imaging analysis.**

- **Fluorescence analysis------ The early studies of polymer blends by using this type of techniques were developed mainly by Morawetz [1] and Frank [2] . For example, Polymer A bearing chromophore can form excimer by itself when one of an excited state chromophore approaches another chromophore at ground state. However, if it is diluted with polymer B, which has no chromophore on the polymer chain, the intensity of the excimer fluorescence will be weakened. A study on blends of poly(2-vinyl naphthalene) (PVN) / PS clearly demonstrated the molecular weight influence on the compatibility of the system. Especially at lower content of PVN (~0.2%), the change in Tg is so small that it can not be seen with DSC or DMA. But It can be observed with fluorescence techniques. Click here to view another type of application of fluorescence**

technique.

- **ESCA------ This technique haven been widely used to study the surface of polymers and polymer blends [3,4]. Generally, in multicomponent polymer blends or copolymers the homopolymer constituent or block having the lower surface energy will migrate to the surface of the material [5]. It is very useful when combined with the other techniques such as FTIR and thermal analysis. Click here to see a surface study of PCL/PVC with the use of ESCA and more about ESCA.**

- **SAXS and SANS------ For an incompatible two homopolymer blends, addition of a third component, preferentially block or graft copolymer, miscible ternary blends can be formed with the right choice of the third component, which is called compatibilizer. These copolymers usually reside at the interface below the critical micelle concentration. The interface of the blends can be studied by many techniques such as welding cleavage experiments, method of neutron reflectivity and SAXS / SANS. Here are few examples of SAXS application on polymer blends.**

Named a few, there more techniques like FTIR, ATR-FTIR, Acoustic Spectroscopy, viscoelastic measurements, AFM etc. that can be used to study polymer blends. There are always new techniques being developed for scientific study.

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Ultraviolet–visible near-field microscopy of phase-separated blends of polyfluorene-based conjugated semiconductors

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We have used fluorescence scanning near-field microscopy to characterize polymer blends for electroluminescent applications, and thereby identify compositional nonhomogeneities. In particular, we have focused on the binary system constituted by poly(9,9′-dioctylfluorene-alt-benzothiadiazole) and poly(9,9′-dioctylfluorene) (PFO), known to give efficiencies of up to 22 cd/A in light-emitting devices with suitable electrodes. Our primary aim was the assignment of the morphological features revealed in shear-force and atomic-force images of spin-coated films, and suggestive of phase separation on a 300-nm-length scale. From analysis of the fluorescence images (325 and 488 nm excitation), and quantitative correlation of optical and topographic data, we identify the raised features with PFO-rich regions. However, the limited variation in fluorescence intensity reveals a high extent of mixing within each phase on the length scale accessible in our experiment, approximately 100 nm for our focused-ion-beam-processed probe apertures. © *2001 American Institute of Physics.* [DOI: 10.1063/1.1389822]

Conjugated polymers provide a class of film-processible semiconductors with significant potential for use in optoelectronic devices, such as light-emitting diodes (LEDs) and photovoltaic cells. Although devices featuring homogeneous active layers display already good performance in terms of electroluminescence efficiency and operating voltage, the use of blends of different electroactive polymers is gaining increasing attention.[1,2] The possibility of blending different semiconductors is a useful property of solution-processible materials, such as conjugated polymers, and allows further improvement of device performance by enabling both selection of the optimum material for each relevant process (charge transport, charge injection, and luminescence), and also fine tuning of the overall device performance by control of the concentration. An important aspect of the physics of these systems is dictated by the generally low entropy of mixing of polymers, which leads to phase separation on length scales ranging from a few nanometers to several microns.[3] Understanding the nature of this phase separation is highly desirable for both quantitative description of device operation, and further performance optimization. For example, the attainment of *vertical* phase separation, so as to have a phase enriched in an electron transporting polymer close to the cathode and a hole transporting polymer close to the anode, would be of considerable interest for controlling charge collection in photovoltaic devices,[2] as well as position and extent of the exciton recombination region in LEDs.

Depending on the length scale involved, investigations can be carried out by means of different microscopies, and in particular with optical probes in the far field, for features with typical dimensions of a micron or larger. Optical probes, such as fluorescence or Raman microscopy, are usually preferable to atomic-force microscopy (AFM) as they are more chemically specific. A shortcoming of conventional far-field spectroscopies, however, is that they cannot provide information on features with dimensions below the classical Abbe diffraction limit. This limit can be overcome by scanning near-field optical microscopy (SNOM),[4] which, furthermore, also provides topographic information to enable a correlation with the results of AFM.

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Here, we investigate phase separation in blends of polyfluorene derivatives, which are currently attracting interest because they appear to offer the best combination of desirable properties, namely: color range, high efficiency, low operating voltage, and device lifetime.[5] In particular, we focus on binary composites of the green-emitting poly(9,9′-dioctylfluorene-alt-benzothiadiazole) (F8BT) and of the blue-emitting poly(9,9′-dioctylfluorene) (PFO). We have previously investigated the demixing properties of this system via far-field optical spectroscopy and tapping-mode AFM.[6] However, although AFM images provided evidence of phase-separated surface-relieved domains, with lateral dimensions of 200–300 nm, we could not identify the major component of these regions, owing to lack of chemical specificity of the AFM probes.

In the present letter, we show that this issue can be resolved through the use of SNOM. From analysis of fluorescence images and quantitative correlation of optical and topographic data, we identify the raised features with PFO-rich regions. However, the limited variation in fluorescence intensity reveals a high extent of mixing within each phase.

The blend studied contains 25% by weight F8BT in PFO, and was prepared by spin coating a xylene solution of the polyfluorenes onto indium–tin–oxide (ITO) -coated glass substrates, previously prepared with a thin film of the hole injection/transport polymer poly(ethylenedioxythiophene) doped with poly(styrene sulphonic acid) (PEDOT:PSS), which is used in polymer LEDs to increase the anode work function.[7]

We used two different optical fibers for the fabrication of the SNOM probes: a single-mode glass fiber for 488 nm excitation, and also a fiber with a pure silica core and a fluorine-doped silica cladding, designed for single-mode transmission at 800 nm, but able to provide high optical throughput at 325 nm. We prepared the probes by first etching the fibers in HF via a self-termination process,[8] and then coating the probes with aluminum. Finally, 300 nm of aluminum were focused-ion-beam (FIB) sliced from the very apex of the probe, before drilling, head-on to the tip, a well-defined aperture in the tip of size $\leq$100 nm.[9–11] A FIB image of a representative tip is shown in Fig. 1. The tip–sample distance was controlled via shear-force feedback, which we implemented by means of a quartz-crystal tuning fork.[12] Images were taken by illuminating the samples in the near-field through the fiber tip (estimated tip–sample distance of ~25 nm), and by collecting the far-field fluorescence in a reflection geometry using a 0.25 numerical aperture microscope objective. We also used two holographic notch filters or a high-pass filter to reject 488 or 325 nm excitation, respectively. The fluorescence was detected with a photon-counting photomultiplier system.

Topographic and fluorescence images with 488 nm excitation are presented in Figs. 2(a) and 2(b). Note that 488 nm excitation results in selective absorption by F8BT,[6] and that in order to facilitate correlation of fluorescence and topography, the intensity scale in Fig. 2(b) is inverted, so that regions of intense fluorescence appear black. The topographic image reveals a rich surface structure, suggestive of phase separation, with one phase forming circular regions 200–300 nm in diameter, protruding from the surface of the film, in

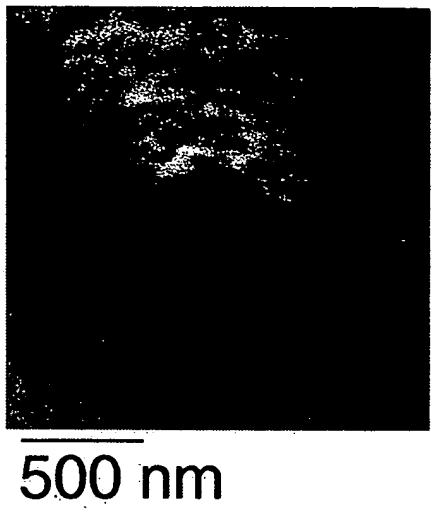

FIG. 1. Focussed-ion-beam (FIB) image of a representative SNOM probe produced by FIB milling and drilling.

agreement with previous AFM studies.[6] Such protruding regions correlate with the areas of weaker fluorescence, indicating that they contain a smaller proportion of F8BT than the other phase. Note, however, that even in the "low fluorescence" regions, we detect some F8BT emission (30%–40% of maximum), implying the presence of F8BT also in PFO-rich regions. This is also consistent with far-field photoluminescence measurements, which suggest some degree of intermixing on a length scale smaller than the Förster transfer radius (5.3 nm).[6]

SNOM images of the same sample, but with excitation at

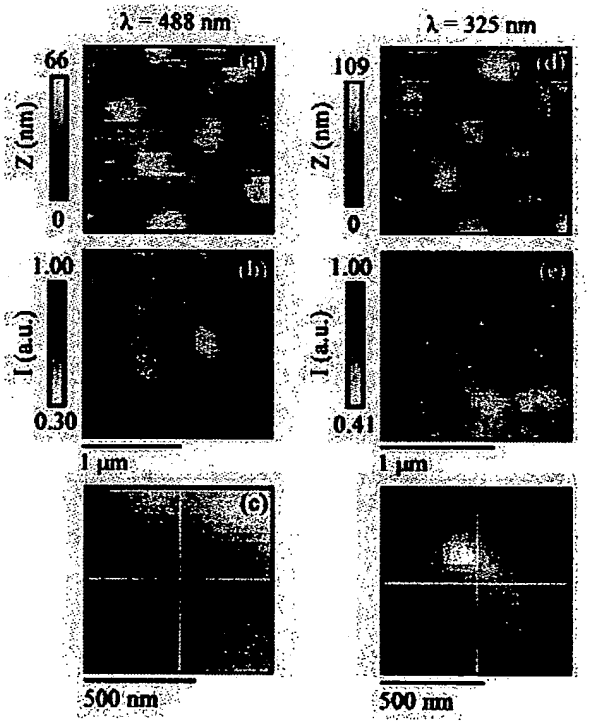

FIG. 2. (Color) (a) and (d) shear-force topography and (b) and (e) SNOM fluorescence of a PFO/F8BT blend thin film, measured using (a) and (b) 488 nm excitation and (d) and (e) 325 nm excitation [note inverted contrast in (b) and (e)]. (c) Correlation plot for images (a) and (b). (f) Correlation plot for images (d) and (e).

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325 nm, are presented in Figs. 2(d) and 2(e). The topographic image is similar to 2(a), again revealing circular regions about 300 nm in diameter, protruding from the surface. Since 325 nm excitation is absorbed predominantly in F8BT, it is not surprising that the results are qualitatively similar to those in Fig. 2(b) [note the inverted contrast in 2(e) as well]. We also tried to detect emission from PFO, by collecting the SNOM fluorescence with bandpass filters (430 and 470 nm) tuned on PFO emission, but we could not detect any signal.

Interpretation of SNOM images with height variations greater than 10 nm should always consider the possibility of topography-induced artifacts which may result from a variation in the distance between the SNOM aperture and the sample surface, as the tip scans over the sample. The most likely scenario is for the tip motion to underestimate variations in the sample topography (particularly given the blunt nature of the probes; see Fig. 1), in which case protruding areas will appear more intense. Note that this is in direct contrast to the pattern observed here. However, further evidence for the integrity of SNOM results can be obtained via quantitative correlation of topography and fluorescence.

For each pair of shear-force topographic $T(\mathbf{r})$ and fluorescence $F(\mathbf{r})$ images, we have obtained a correlation plot $C(\mathbf{r})$, given by

$$C(\mathbf{r}) = \int \bar{T}(\mathbf{r}'+\mathbf{r})\bar{F}(\mathbf{r}')\mathbf{dr}', \tag{1}$$

where $T(\mathbf{r})$ and $F(\mathbf{r})$ have been normalized to give $\bar{T}(\mathbf{r})$ and $\bar{F}(\mathbf{r})$, respectively, and the integral calculated via fast Fourier transforms. The resulting correlations are presented in Figs. 2(c) and 2(f). White and black regions correspond to a displacement of the optical image with respect to the topographic one, resulting in a correlation (white) or anticorrelation (black) of protruding regions with areas of intense fluorescence. In Fig. 2(c) the distinctive black circular region, centered at a displacement of ~40 nm, confirms that the protruding regions of the film are less fluorescent. The white region, indicative of correlation for displacements of about 400 nm, is poorly defined; furthermore, we should note that unambiguous interpretation of such large correlation length scales would require larger scan areas. We take this positive correlation to represent the underlying regularity in the polymer film. The same pattern is repeated for 325 nm excitation [Fig. 2(f)], although in this case the displacement between protruding regions and areas of less intense fluorescence in the polymer film is greater, approximately 200 nm. The region of positive correlation is a poorly defined white crescent, again suggestive of an underlying regularity in the sample. The 200 nm displacement between optical and topographic images is consistent with the form of the SNOM probe used for these experiments (the tip shown in Fig. 1)—a displacement between topographic and fluorescence images has been observed before,[13] and has been attributed to the presence of a protruding region on the probe (which could be an edge of the flat probe end in this case), which is displaced from the aperture. Indeed, the observation of such a displacement in these images provides a strong argument for rejection of topographic artifacts.

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Excimer Fluorescence as a Molecular Probe of Polymer Blend Miscibility. 9. Effects of Guest Concentration and Annealing in Blends of Poly(2-vinylnaphthalene) with Poly(cyclohexyl methacrylate)

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ABSTRACT: Excimer fluorescence from poly(2-vinylnaphthalene) (viscosity-average molecular weight of 17 000) was used to study the morphology of blends with poly(cyclohexyl methacrylate) prepared by solvent casting from toluene at 295 K and annealing at 413 K. A lattice model involving three-dimensional electronic excitation transport (EET) was used to interpret the ratio of excimer-to-monomer fluorescence, I_D/I_M, for P2VN concentration >60 wt %, while an intramolecular one-dimensional EET model was applied to P2VN concentration <25 wt %. Before annealing there is a much higher probability of formation of both intramolecular and intermolecular excimer-forming sites relative to the annealed blend. Furthermore, the blends with P2VN concentration below 70 wt % approach the equilibrium morphology characteristic of 413 K much faster than those with higher concentrations. A concave-downward curvature in I_D/I_M with increasing P2VN concentration indicates a phase-separated system, while a concave-upward curvature is found for miscible blends. A linear relationship between I_D/I_M and P2VN concentration can result for miscible blends when there are no intermolecular excimer-forming sites or for immiscible blends, when the volume fraction of the rich phase is much greater than that of the lean phase.

I. Introduction

Excimer fluorescence is an effective and sensitive morphological tool for the study of miscibility of an aromatic vinyl polymer with a nonfluorescent host polymer.[1-16] A convenient measure of the degree of mixing at the molecular level is the photostationary excimer-to-monomer fluorescence ratio, I_D/I_M. One problem with establishing excimer fluorescence as a quantitative tool, however, is that there are two photophysical effects that are difficult to separate: the population of traps and the mode by which these traps are sampled. In general, each pendant aromatic chromophore can absorb unpolarized light, and the excitation energy can migrate among the ensemble of chromophores before eventually undergoing nonradiative or radiative decay from a pendant chromophore or lower energy excimer trap.[17] The difficulties in the interpretation of changes in I_D/I_M with respect to blend thermodynamics stem from the existence of several types of excimer-forming sites (EFS) and the complex pathway of electronic excitation transport (EET) leading to excimer fluorescence. The degree of chain coiling and the extent of guest polymer aggregation will influence both the EFS population and the EET mode by which these traps are sampled. An understanding of the coupled interaction between the number and types of EFS traps and the nature of the excitation transport process is essential to being able to describe the chain structure and the blend morphology.

Our objective is to establish a quantitative understanding of the photophysical properties of the blend of poly(2-vinylnaphthalene) (P2VN) with poly(cyclohexyl methacrylate) (PCMA). To set the stage for this study, we first review the highlights of previous photophysical work on polymer blends and related systems. Initial photophysical work was phenomenological and was based on the simple assumption that the observed I_D/I_M was proportional to the local concentration of aromatic rings. Phase separation was thus expected to lead to an increase in I_D/I_M. Experiments were designed based upon the predictions of equilibrium Flory–Huggins thermodynamics.[18]

The first group of experiments by several investigators on relatively high molecular weight polymers emphasized enthalpic contributions to the free energy of mixing. Gashgari and Frank[4-6,9] investigated low-concentration (0.2 wt %) blends of P2VN in a homologous series of poly(alkyl methacrylates) and observed I_D/I_M to pass through a minimum when the guest and host solubility parameters were equal. Similar results were found for poly(acenaphthylene) and poly(4-vinylbiphenyl) dispersed in the same homologous host matrix series. In addition, Soutar[19] observed a minimum in I_D/I_M as a function of solvent solubility parameter for poly(1-vinylnaphthalene) and poly(1-vinylnaphthalene-*co*-methyl methacrylate) in toluene/methanol and toluene/cyclohexane mixed solvent systems. A solvent series was also used by Li et al.[20] to examine I_D/I_M for polystyrene (PS) labeled with pyrene groups at regularly spaced intervals. In each of these cases, the value of the solubility

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parameter for the guest polymer corresponding to the observed I_D/I_M minimum agrees quite well with literature values or estimates based upon molar group additivity calculation.

The second group of experiments emphasized entropic contributions to the free energy of mixing. The important variable is the molecular weight, which Semerak and Frank[6,11,14] examined for P2VN in both polystyrene and poly(methyl methacrylate) (PMMA) host matrices. The photophysical analysis was still phenomenological with emphasis placed on changes in I_D/I_M as a function of guest and host molecular weight. However, quantitative calculations of the complete binodal curves using Flory–Huggins theory allowed rationalization of the molecular weight dependence of the apparent microphase separation. The sensitivity of the excimer probe to local blend morphology is demonstrated by the fact that increases in I_D/I_M consistently preceded changes in the visual appearance of the blends as conditions were altered toward immiscibility.

The third group of experiments moved beyond the phenomenological stage and made the first attempt at treating the photophysics on a quantitative basis. The key element of this work was the development of simple models for EET in limiting concentration regimes. Gelles and Frank[12,13] employed the miscible blend PS/poly(vinyl methyl ether) (PVME) to separate the contribution of EFS population and EET efficiency. A one-dimensional random walk model was used to explain the PS molecular weight dependence of I_D/I_M for 5 wt % PS blends. A three-dimensional lattice model was used to interpret the I_D/I_M results for blends with guest concentration >60 wt %. With a two-phase model, they were also able to fit the photostationary data for the immiscible blends cast from tetrahydrofuran (THF). The kinetics of microphase separation were found to be in good agreement with the de Gennes–Pincus theory[21] of spinodal decomposition.

Recent studies have been directed toward nonequilibrium aspects of the solvent-casting process. Frank and Zin[22] observed that the initially cloudy, phase-separated PS/PVME blends cast from THF became clear upon annealing at 384 K and attained the same I_D/I_M values as those of the miscible PS/PVME blends cast from toluene. The role of the THF in setting up the morphology of the PS/PVME blend is uncertain, but it appears that the blend approaches its equilibrium morphology during the annealing process. Recently, Gashgari and Frank[23] examined the influence of casting temperature on blends of P2VN with poly(*n*-butyl methacrylate) (PnBMA) and PMMA with guest concentration below 10 wt %. They established that solvent casting at temperatures greater than T_g for the blend/solvent system, followed by rapid quenching to a temperature below T_g, can quench in the morphology characteristic of the casting temperature. Annealing experiments performed above T_g on blends cast below T_g allowed monitoring of the approach to equilibrium.

The present paper is an extension of the Gashgari and Frank[9,23] study in which the effect of annealing at a temperature greater than T_g is investigated for blends of 71 000 M_v P2VN with PCMA of molecular weight 35 000 over the guest concentration range of 0.1–100 wt %. According to classical differential scanning calorimetry measurements, the PCMA appears to be miscible with P2VN over all proportions. Our first objective is to analyze I_D/I_M as a function of annealing time with two photophysical models. For results from blends with 60 wt % or greater P2VN concentration, the Gelles–Frank three-dimensional lattice model should apply. For P2VN concentration <25 wt %, we will test the one-dimensional Fitzgibbon–Frank model.[24] We are particularly interested in the change in the probability of formation of intramolecular and intermolecular EFS as the blends are annealed. The second objective is to use transient-state fluorescence to investigate the efficiency of EET and correlate with the results derived from the photostationary-state models. Finally, we will address the kinetics involved in attaining an equilibrium morphology and discuss the general behavior of the observable I_D/I_M as a fingerprint for blend miscibility.

II. Experimental Section

A. Materials. Toluene (Aldrich, spectrograde, for fluorescence spectroscopy) was vacuum distilled and passed through a silica gel column prior to use. P2VN (71 000 viscosity-average molecular weight, $M_w/M_n = 1.30$), the same bulk thermally polymerized material described previously,[25] was purified by repeated precipitation from toluene into distilled methanol. PCMA ($M_n = 35\,000$) samples were obtained from Aldrich and purified by repeated precipitation from toluene into distilled methanol.

The solid P2VN/PCMA blends were prepared with toluene as the casting solvent. After the samples were air-dried for 24 h, the initial photostationary-state fluorescence spectra were taken, and the samples were placed in a vacuum oven for annealing. The samples were annealed at 413 K for 12, 24, 48, and 96 h, with spectra being taken at room temperature at the end of each annealing period. To minimize the possibility of oxidative decomposition of the sample during annealing, the oven was evacuated and back-filled several times with nitrogen. The final films were approximately 25 μm thick.

B. Instrumentation. The photostationary-state experimental apparatus and methods of P2VN blend investigation have been described elsewhere.[26] Transient fluorescence lifetime measurements were performed on a Photochemical Research Associates nanosecond time-correlated single-photon-counting spectrometer, Model PRA 3000. All of the samples were excited at 290 nm with a 10-nm band-pass excitation monochromator filter. Monomer fluorescence from P2VN, typically observed between 310 and 350 nm, was selectively collected with a Toshiba UV340 10-nm band-pass filter. Instrumental response functions of 1.5-ns fwhm were routinely achieved by collecting the scattered stray light of a Ludox scattering solution at 340 nm, the peak of the monomer emission envelope.

C. Analysis. The excimer-to-monomer fluorescence ratio was obtained from intensities measured in regions where overlap between excimer and monomer emission could be neglected. Fluctuations in xenon lamp intensity were corrected for by scaling the data to the exciting beam intensity. The fluorescence spectra were corrected for monochromator and detector response with a tungsten-in-quartz lamp. Transient fluorescence profiles were fitted with a multiexponential trial function by the method of iterative reconvolution with the lamp profile using a nonlinear χ^2 minimization algorithm of Marquardt.[26] The quality of fit was judged by the reduced χ^2 criterion, visual inspection of the deviations in the weighted residuals, and the profile of the autocorrelation function.

III. Results

A. Annealing Measurements. The I_D/I_M results for the P2VN/PCMA blends annealed at 413 K are presented as a function of P2VN guest concentration in Figure 1. Results from the four annealing periods are illustrated along with those from the P2VN/PCMA blends air dried for 24 h. The I_D/I_M results for 96 h of annealing are identical with those obtained for 48 h. For the blends that were air-dried only, I_D/I_M is essentially a linear function of P2VN weight percent for P2VN concentration below 80 wt %. The P2VN neat film I_D/I_M

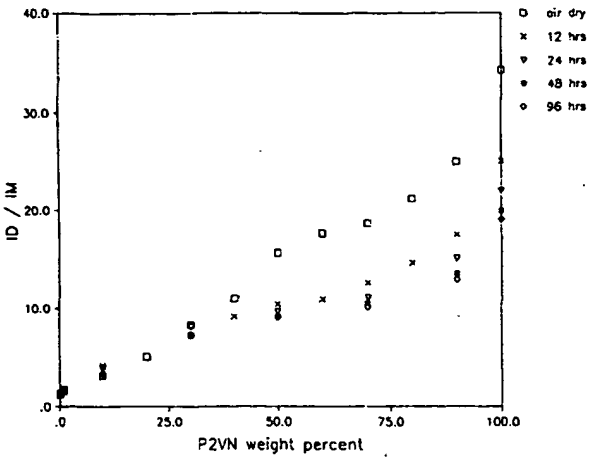

Figure 1. Observed I_D/I_M fluorescence ratio as a function of P2VN guest concentration for blends of P2VN(70 000)/PCMA(35 000) cast with toluene at 295 K. The blends are annealed for a maximum of 96 h at 413 K. The number beside each curve indicates the annealing time. All of the blends remain optically clear after 96 h of annealing. Standard deviations are <10% in this and subsequent plots of I_D/I_M.

value equals 38, which is about 10% lower than that determined by Semerak.[15] For blends with guest concentration below 30 wt %, I_D/I_M is independent of annealing time. All of the films are optically clear after air-drying for 24 h, and they remain clear after each annealing period.

The significant point is that I_D/I_M decreases with annealing time for each P2VN concentration, including the neat film. This suggests that the P2VN configuration in the original cast film is not at equilibrium but frozen in a morphology characteristic of a P2VN/toluene binary system. Semerak and Gashagari[8,9,14] have found that as high as 20 wt % of solvent can remain trapped inside the polymer matrix after air-drying at room temperature for PS and PMMA hosts having glass transition temperatures of 373 and 382 K, respectively. Therefore, it is possible that there could be a large amount of residual toluene left in the blends after 24 h of air-drying.

B. Transient Fluorescence Lifetimes. Transient studies of the P2VN/PCMA blends were carried out at room temperature. The decay lifetime of the naphthalene monomer was measured at 340 nm with excitation at 290 nm. In general, the monomer fluorescence decay can be adequately described by a triple-exponential trial function. Tables I–III present the fitted lifetimes and preexponential factors for the different P2VN composition blends that were air-dried and annealed for 12 and 48 h, respectively. These lifetimes cannot be arbitrarily associated with physically distinct excited states. Fredrickson and Frank[27] have shown that a configuration with only a single excimer trap state among many donors can result in a nonexponential decay due to the influence of EET. The form of this nonexponential decay may be approximated as a multiexponential. Our results simply reflect three dominant deactivation pathways for the excited P2VN monomer among the many possible pathways in the complex photophysical scheme.

These dominant deactivation pathways for the monomer have average lifetimes of ca. 5, 25, and 80 ns with intensities of 10%, 25%, and 65%, respectively. The intensity ratios remain relatively constant for the different P2VN composition blends whether or not the blends were annealed. For both the air-dried and annealed blends, the lifetimes decrease with increasing P2VN guest concentration. The lowering of the lifetimes suggests a faster deactivation of the monomer. This is possibly associated with an increase in the efficiency of EET and the formation of more EFS at high guest concentration.

In the absence of a comprehensive photophysical decay scheme for the P2VN/PCMA blend system, we choose to represent the transient results in the form of a single effective decay lifetime, $\langle\tau\rangle$, as a function of blend composition for each of the air-dried and annealed blends. This has been shown to be a good phenomenological approach to relate changes of blend morphology and local polymer interaction to fluorescence results. The effective lifetime is given by

$$\langle\tau\rangle = \sum A_i\tau_i^2 / \sum A_i\tau_i \qquad (1)$$

where A_i and τ_i are the individual preexponential factor and lifetime. Figure 2 illustrates the calculated $\langle\tau\rangle$ as a function of P2VN guest concentration for blends that were air-dried and annealed for 12 and 48 h. For blends with P2VN concentration below 50 wt %, $\langle\tau\rangle$ is essentially constant within experimental error.

IV. Discussion

A. Three-Dimensional Electronic Excitation Transport. The photostationary fluorescence observable may be related to fundamental photophysical quantities by

$$\frac{I_D}{I_M} = \frac{Q_D}{Q_M}\left[\frac{1-M}{M}\right] \qquad (2)$$

where Q_D is the ratio of the fluorescence decay constant to the total decay constant for the excimer and Q_M is the analogous ratio for the monomer. The quantity M is the probability that a photon absorbed by the aromatic vinyl polymer guest will decay along a radiative or nonradiative monomer pathway. Thomas and Frank[16] examined P2VN/PCMA blends and determined that Q_D/Q_M is equal to 0.44 ± 0.08. Moreover, Q_D/Q_M is independent of the host molecular weight, and thus the quantity $(1-M)/M$ is the only factor that influences I_D/I_M.

Equation 2 has been applied to polymer blends in two ways. One approach has been to employ an analytical expression for M, typically containing one or two adjustable parameters, that is thought to be applicable at high or low concentrations of the aryl vinyl polymer. Experimental I_D/I_M results are then fit with eq 2. This has been done for miscible PS/PVME blends for which the morphology,[12,13] i.e., the random mixing, is relatively uncomplicated. An alternate approach has been taken for the much more complex case of a phase-separated blend. This situation requires that a set of reference data consisting of I_D/I_M as a function of concentration for a miscible blend of the same components be obtained initially. It is then assumed that the fluorescence behavior of the phase-separated system is a volume-weighted average of contributions to M, and thus I_D/I_M, from rich-phase and lean-phase components.

We begin by treating the P2VN/PCMA blend as miscible and analyze the high-concentration results with a three-dimensional spatially periodic lattice model developed by Gelles and Frank,[12,13] referred to as the GF model. This model describes three-dimensional hopping between neighboring sites on a periodic lattice with a distance dependence corresponding to the Förster energy-transfer mechanism for the case of no emission or trapping. The size of the lattice site is taken equal to the size of the P2VN repeat unit; the PCMA segments are then broken up to fit into the same lattice. Under this assumption, the separation distance between adjacent elements

Table I
Transient Results for Air-Dried P2VN/PCMA Blends

P2VN wt %	$A(1)$	$\tau(1)$	$A(2)$	$\tau(2)$	$A(3)$	$\tau(3)$	$\langle\tau\rangle$	χ^2
10	0.269	6.13	0.157	25.21	0.093	88.03	60.27	1.24
20	0.296	5.27	0.135	25.61	0.099	88.57	63.39	1.32
30	0.297	4.18	0.136	23.34	0.115	84.90	64.05	1.14
40	0.270	4.23	0.144	24.97	0.113	85.24	63.69	1.10
50	0.258	5.08	0.135	26.85	0.107	84.26	61.83	1.12
60	0.257	5.16	0.156	25.59	0.122	81.22	59.97	1.25
70	0.236	4.72	0.153	24.04	0.113	79.37	58.54	1.07
80	0.229	5.17	0.145	24.14	0.113	76.74	56.57	1.12
90	0.231	5.48	0.143	24.92	0.106	76.97	55.72	1.05
100	0.217	4.95	0.146	22.67	0.104	73.62	53.47	1.14

Table II
Transient Results for P2VN/PCMA Blends Annealed for 12 h

P2VN wt %	$A(1)$	$\tau(1)$	$A(2)$	$\tau(2)$	$A(3)$	$\tau(3)$	$\langle\tau\rangle$	χ^2
10	0.207	5.82	0.104	25.32	0.077	88.65	63.73	1.09
20	0.191	5.67	0.081	26.86	0.074	88.07	65.28	1.08
30	0.179	4.67	0.085	24.04	0.078	84.68	64.45	1.04
40	0.156	5.16	0.085	26.51	0.072	85.30	63.96	0.93
50	0.135	6.23	0.070	28.34	0.066	83.12	62.25	1.18
60	0.125	4.90	0.065	26.06	0.053	80.37	59.15	1.12
70	0.133	5.81	0.075	28.28	0.057	81.08	57.18	0.99
80	0.107	5.13	0.062	24.49	0.046	77.15	55.92	0.90
90	0.107	4.82	0.063	23.31	0.044	74.93	53.87	1.07
100	0.085	3.78	0.039	19.97	0.026	70.90	49.95	1.20

Table III
Transient Results for P2VN/PCMA Blends Annealed for 48 h

P2VN wt %	$A(1)$	$\tau(1)$	$A(2)$	$\tau(2)$	$A(3)$	$\tau(3)$	$\langle\tau\rangle$	χ^2
10	0.195	5.65	0.102	25.70	0.072	88.42	62.84	1.05
20	0.186	5.49	0.077	27.12	0.071	88.40	65.75	1.01
30	0.165	4.90	0.071	25.79	0.069	85.07	64.70	0.98
40	0.150	4.78	0.067	26.13	0.063	84.77	64.28	1.15
50	0.129	4.52	0.068	25.35	0.057	82.92	62.31	1.21
60	0.121	5.07	0.061	24.47	0.045	80.33	57.68	0.95
70	0.119	4.96	0.053	23.11	0.039	78.21	55.45	1.29
80	0.105	4.55	0.050	22.79	0.032	75.37	52.10	0.97
90	0.099	4.76	0.043	21.96	0.030	74.20	51.66	1.35
100	0.076	3.15	0.034	18.91	0.021	70.11	49.32	1.10

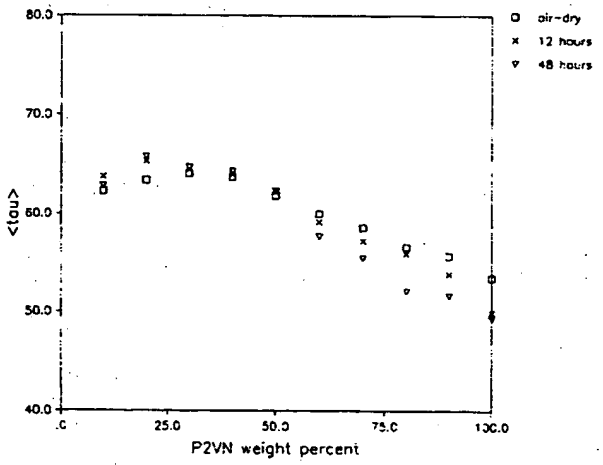

Figure 2. Calculated effective lifetime, $\langle\tau\rangle$, for monomer deactivation as a function of P2VN guest bulk concentration. All of the transient fluorescence results can be adequately characterized by a triple-exponential fitting function. The deviation of $\langle\tau\rangle$ from a constant value for blends with P2VN concentration >50 wt % suggests an enhancement of monomer deactivation possibly due to more EFS formed accompanied by an increase in the dimensionality of EET. The number beside each smooth line drawn through the data indicates the annealing time.

in the lattice will then be constant, although the number of P2VN rings next to any given ring will depend on concentration. It is further assumed that transfer can only take place between rings that are nearest neighbors, that the rate of transfer between two neighbors is constant with composition, and that the sum of the rates of transfer to each of the nearest neighbors equals the net rate of transfer from a given ring.

The quantity M takes the form

$$M = \frac{\alpha - q\alpha}{\alpha + q\left[\frac{1-\alpha}{2-q_D}\right]} \tag{3}$$

where q is the ring fraction of EFS and is related to the diad trap fraction, q_D, by $q = q_D(2 - q_D)$. The quantity α is the fraction of times that monomer emission occurs before energy transfer and is given by

$$\alpha = (1 + N\nu W\tau)^{-1} \tag{4}$$

where N is the number of nearest neighbors of the emitting chromophore in the lattice, W is the uniform rate of nearest-neighbor EET, τ is the measured lifetime of the excitation in the absence of energy transfer, and ν is the volume fraction of fluorescent polymer. The diad trap fraction, q_D, is expressed as the sum of an intramolecular part arising from trans,trans meso rotational diads, $q_{D,intra}$, and an intermolecular portion due to segmental association between different chains, $q_{D,inter}$

$$\begin{aligned} q_D &= q_{D,intra} + q_{D,inter} \\ &= q_{D,intra} + (N-2)\Omega_D\nu \end{aligned} \tag{5}$$

The quantity Ω_D is the probability that chromophores in two adjacent lattice sites are in an intermolecular EFS.

In order to fit the concentration results for the air-

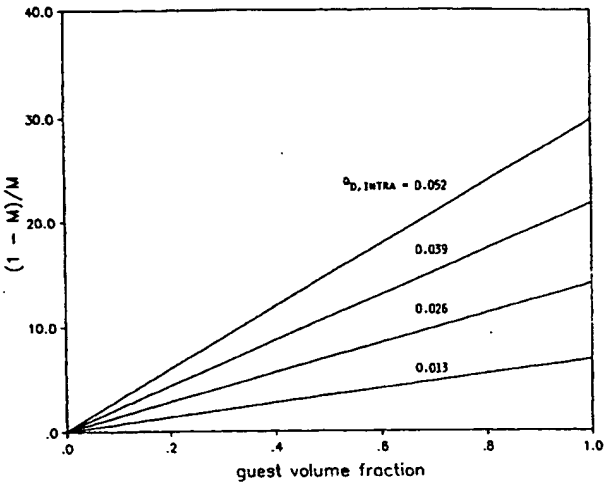

Figure 3. Behavior of I_D/I_M as a function of guest concentration as described by the GF 3-D model for systems with no intermolecular EFS. The number beside each curve indicates the annealing time. The results of the fit are summarized in Table IV.

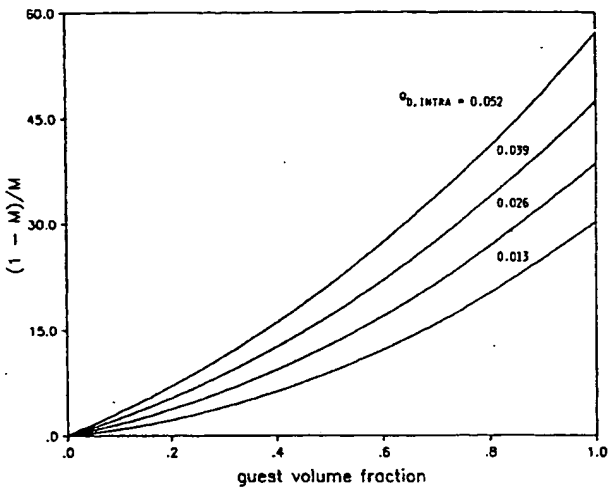

Figure 4. Behavior of I_D/I_M as a function of guest concentration as described by the GF 3-D model for systems with a 0.005 probability for intermolecular EFS formation. The number beside each curve indicates the intramolecular EFS population.

dried and annealed P2VN/PCMA blends, we have to specify two of the parameters. The quantity $W\tau$ in Förster dipole–dipole resonant transfer theory is assigned the value corresponding to an average intermolecular chromophore separation of 11.75 Å, which is equal to the Förster radius, R_0, for a neat P2VN film. We assume that the minimum P2VN concentration at which EET becomes three-dimensional corresponds to this same average intermolecular chromophore separation. At this separation, the probability of transfer between two rings is equal to the probability of monomer emission. If we assume the chromophore separation to be approximately equal to $[1/(\text{ring concentration})]^{1/3}$, we obtain the ring concentration corresponding to the onset of three-dimensional EET. From these calculations, we found the P2VN volume fraction to be 0.52. It is interesting to note that similar calculations performed for PS/PVME and P2VN/PnBMA blends indicate that the minimum guest concentration for three-dimensional EET should be 0.60 and 0.14, respectively. Finally, N is taken to be ca. 10. This leaves $q_{D,intra}$ and Ω_D as the parameters to be fitted.

It is useful to illustrate graphically the sensitivity of the GF model to variation in the magnitude of $q_{D,intra}$ and Ω_D. Since both parameters describe the probability of forming more EFS, an increase in either should result in an increase in I_D/I_M. The effect of these parameters on the efficiency of EET in terms of increased dimensionality, however, is only of second order. Exciton transport is already assumed to be three-dimensional, and the model is expected to be applicable to blends with high guest concentration. It is the frequency of sampling an EFS and the trapping of the exciton that are enhanced.

The behavior of I_D/I_M, represented in the form of $(1 - M)/M$ from eq 2, as a function of guest concentration for a varying $q_{D,intra}$ is illustrated in Figures 3 and 4. In these calculations, we assumed N to be 10 and $W\tau$ to be 51. The latter value has been found by Semerak and Frank[15] to yield a total EFS diad fraction of 0.072 for a neat P2VN film. By comparison, the total EFS diad fraction for pure polystyrene is 0.33. The small EFS fraction for P2VN seems plausible given the low symmetry of the naphthyl pair in forming an EFS. Figure 3 represents the case in which there are no intermolecular EFS, i.e., $\Omega_D = 0$. The linear increase in I_D/I_M with P2VN volume fraction for any value of $q_{D,intra}$ reflects the enhanced sampling of intramolecular EFS on different

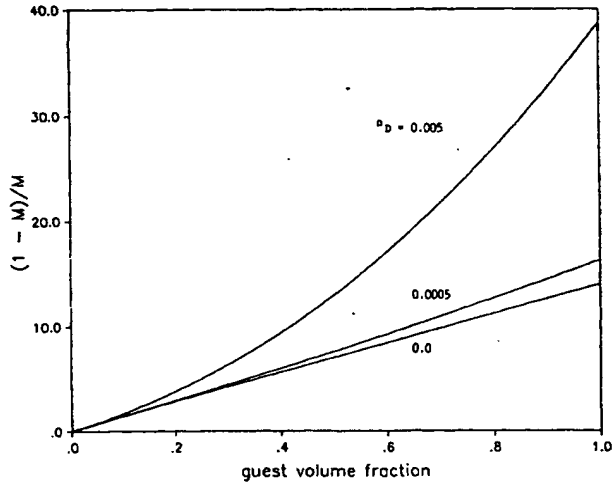

Figure 5. Behavior of I_D/I_M as a function of guest concentration as described by the GF 3-D model for systems with a constant population of intramolecular EFS and different probabilities for intermolecular EFS formation. The number beside each curve indicates the probabilities for forming intermolecular EFS.

chains due to three-dimensional EET. For $\Omega_D = 0.005$, shown in Figure 4, there is a substantial increase in I_D/I_M for the same values of $\Omega_{D,intra}$ used in Figure 3. This is better illustrated in Figure 5 in which we keep $\Omega_{D,intra}$ constant and vary the magnitude of Ω_D. An exciton migrating along a chain contour may encounter a chromophore that can be in an EFS configuration with either an adjacent intramolecular chromophore or an intermolecular chromophore.

The results of fitting the GF model to I_D/I_M for P2VN/PCMA blends with P2VN concentration >50 wt % are presented in Table IV and illustrated in Figure 6. The model fitted the high-concentration data quite well for the air-dried blends and all of the annealed blends. Both $\Omega_{D,intra}$ and Ω_D decreased as a function of annealing time. If the lower concentration results are included, we found that the fitting parameters cannot be kept constant over the entire range. Therefore, our choice of P2VN concentration >50 wt % for the applicable range for three-dimensional EET appears to be valid. The magnitude of Ω_D, found to be an order of magnitude lower than that for PS in PVME, seems reasonable by comparison due to the strict geometric requirements necessary for inter-

Table IV
Excimer-Forming Site Concentration after Annealing

annealing time, h	$q_{D,intra}$	Ω_D	q_D[a]
air-dried	0.067	5.5×10^{-3}	0.111
12	0.043	3.9×10^{-3}	0.074
24	0.046	3.6×10^{-3}	0.075
48	0.048	2.9×10^{-3}	0.071
96	0.047	2.9×10^{-3}	0.070

[a] $q_D = q_{D,intra} + (N-2)\Omega_D{}^{\nu}$, where $N = 10$ and ν is assigned the value of 1.0.

molecular excimer formation in P2VN.

The results indicate that the air-dried film contains more intramolecular and intermolecular EFS than the annealed film. We infer that it may be in a nonequilibrium state relative to the annealed film. Upon annealing, the blend undergoes diffusive rearrangement, leading to fewer EFS. In Table IV, we present the total EFS concentration for the neat film using the values of $q_{D,intra}$ and Ω_D from the fit. The most important result is that $q_{D,total}$ starts out higher than the neat film value of 0.072 and approaches a value close to that of the neat film after only a short annealing time. The value of $q_{D,intra}$ after 12 h of annealing is approximately twice the value calculated from rotational isomeric state theory. This may reflect the influence of guest concentration on the chain configuration of P2VN or additional intramolecular EFS traps beyond the trans,trans meso diad.

The decrease of $\langle\tau\rangle$ for guest concentration above 50 wt %, as shown in Figure 2, suggests an annealed blend morphology that allows for more efficient monomer deactivation pathways. It is interesting to note that a 50 wt % P2VN blend corresponds to an intermolecular chromophore separation approximately equal to the Förster transfer radius for P2VN. At this chromophore separation, the dominant mode of EET is suspected to be three-dimensional. The decrease in $\langle\tau\rangle$ might be related to an increase in efficiency of EET due to local rearrangement as the blend is annealed.

We note that I_D/I_M is independent of annealing time for blends with P2VN concentration below 30 wt %. Our question concerns whether or not the guest coils are sufficiently isolated such that EET among the naphthalene chromophores may be treated as quasi-one-dimensional. If so, the value of Ω_D should be much smaller than that found for the high P2VN concentration blends.

A statistical model for strictly one-dimensional exciton migration between nearest neighbors on an isolated polymer chain was originally developed by Fitzgibbon and Frank[24] and will be referred to as the FF model. The FF model treats the equilibrium EFS concentration in the polymer chain as irreversible exciton traps that divide the chain into segments of nontrap sites. In the hypothetical case of an infinitely long polymer chain, M in eq 2 is computed by averaging the value of M for each segment length over the distribution of nontrap segment lengths and is given by

$$M = 1 - q_D - \frac{q_D{}^2}{\tanh(\Gamma)} \sum_{x=1}^{\infty} (1-q_D)^x \tanh(\Gamma x) \qquad (6)$$

where

$$\Gamma = 0.5 \ln\left[\frac{1 + 2W_\tau + (1+4W_\tau)^{1/2}}{2W_\tau}\right] \qquad (7)$$

In eq 7, q_D is the diad fraction of EFS given by eq 5. At the low P2VN concentration for which this model may be appropriate, a first approximation for q_D is simply the intramolecular site fraction calculated from rotational isomeric state theory.

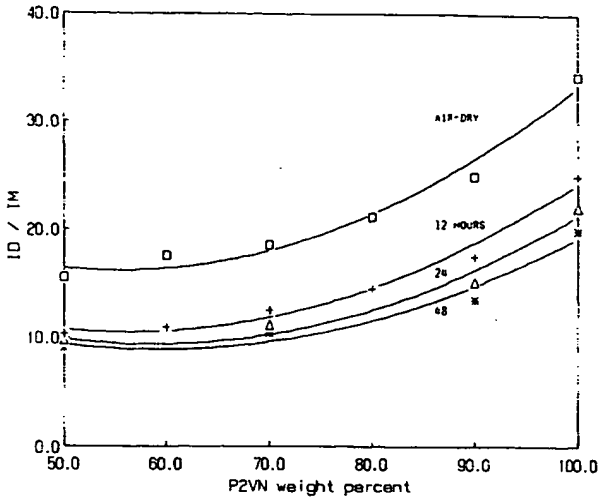

Figure 6. Results of fitting the GF 3-D model to the air-dried and annealed blends with P2VN guest concentration >50 wt %. The number beside each curve indicates the annealing time. The results of the fit are summarized in Table IV.

We set W_τ equal to the Förster value of 51 and $q_{D,intra}$ to 0.026 as we did for the GF model. The latter value was determined for isolated coils of atactic (45% meso) P2VN. The model is applied over all of the I_D/I_M results for blends with <30 wt % P2VN, i.e., the linear portion in Figure 1. We realize that this is an ad hoc way of introducing concentration as a parameter in the one-dimensional model, but it is merely intended to test the sensitivity of this model to results from a quasi-one-dimensional system. The value of Ω_D from the fit is 1.72×10^{-5}, representing a very low probability of intermolecular EFS formation.

B. Annealing Kinetics for P2VN/PCMA Blends. Diffusive rearrangement in a polymer blend depends on the thermal driving force available and the viscosity of the blend. The latter is related to the molecular weight of the blend components, the relative concentration of the polymers, and the amount of residual solvent. During air-drying and annealing, the film composition changes from a ternary system including solvent to that of a binary polymer system. The viscosity of the blend should increase dramatically during this evaporation period, thereby slowing down further changes in local blend morphology.

The thermal driving force is represented approximately by the difference between the annealing temperature, T_a, and the glass transition temperature of the blend, T_g. For the P2VN/PCMA system, the glass transition temperature for different blend compositions follows the Fox equation[28]

$$\frac{1}{T_g(\text{blend})} = \frac{w}{T_g(\text{P2VN})} + \frac{1-w}{T_g(\text{PCMA})} \qquad (8)$$

where w is the weight fraction of P2VN. The annealing experiment was performed at a temperature of 413 K, which is 76 K above the T_g of PCMA and only 8 K above the T_g of P2VN. From eq 8, it is obvious that the thermal driving force for molecular rearrangement will be greater for the lower P2VN concentration blend.

The general slope of curves between I_D/I_M and annealing time drawn through the results shown in Figure 1 for a constant P2VN concentration suggests that a fitting equation of the form

$$R[t] - R[96] = \{R[0] - R[96]\} \exp(-kt) \qquad (9)$$

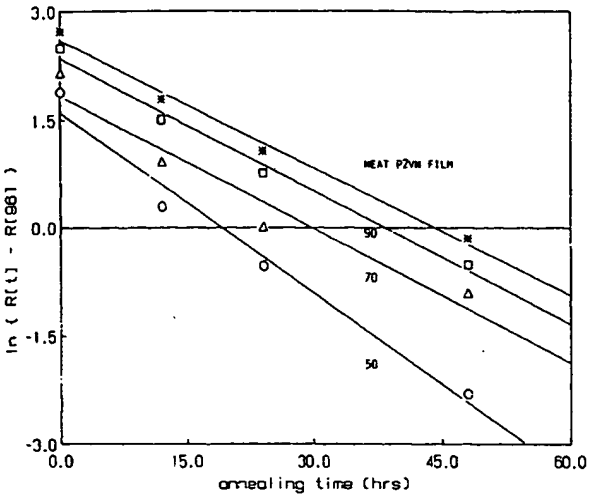

Figure 7. Analysis of the effect of annealing time at 413 K for P2VN/PCMA blends cast at 295 K. The smooth lines drawn through the data represent the use of eq 9 to fit the results.

Table V
Rate Constant for Thermal Diffusive Rearrangement

P2VN wt %	k, h^{-1}	τ, h	$T_a - T_g$°
100	0.059	16.95	8.0
90	0.061	16.39	16.01
70	0.062	16.13	31.12
50	0.084	11.91	45.16

° The T_g is calculated according to the Fox equation (eq 8).

may be appropriate. Here $R = I_D/I_M$ and $R[96]$ is the value of I_D/I_M after 96 h annealing at 413 K, $R[t]$ is the ratio after t hours of annealing, $R[0]$ is I_D/I_M for the room temperature cast blend prior to annealing, and k is the rate constant characterizing the diffusive rearrangement. Representative plots for 50, 70, and 90 wt % P2VN concentration blends and the neat film are presented in Figure 7. In geneal, this semilogarithmic form fits the data quite well over the entire range of annealing times.

The rate constants derived from the plots of Figure 7 are presented in Table V along with the magnitude of the thermal driving force expressed as $T_a - T_g$. It appears that the rate of diffusive rearrangement is limited by the viscosity of the blend until the thermal driving force exceeds 35 K. By comparison in P2VN/PnBMA blends with 10 wt % P2VN, local motion of the polymer with similar time scales occurs at $T_a - T_g = 20$ K. Although thermally induced phase separation occurs for the P2VN/PnBMA system after annealing, the value of $T_a - T_g$ still reflects the magnitude of the thermal driving force required to cause diffusive motion between the guest coils. This suggests that the use of the Fox equation to calculate T_g might be inappropriate for the higher guest concentration blends.

Application of the Fox equation is only appropriate when the blend is homogeneous over the entire range of blend composition. Equation 8 will be inapplicable when the blend is phase separated. We can use the results for the neat P2VN film in Table V as a reference for the following interpretation. For the neat film, thermal annealing at 413 K cannot cause macroscopic phase separation but does provide sufficient driving force for local rearrangement. This type of motion occurs at a time scale equal to ca. 17 h, as shown in Table V. The near-constant rate of diffusive motion for blends with P2VN guest concentration >70 wt % suggests that the thermal driving force for these blends is actually lower than that calculated with eq 8. The local chromophore concentration resembles that of the neat film, resulting in a higher glass transition temperature for the blend.

C. Behavior of I_D/I_M Reflecting the Degree of Blend Miscibility. In this section we wish to examine the general characteristics of plots between I_D/I_M and guest concentration for miscible and immiscible blends. The behavior of I_D/I_M with increasing guest concentration can be classified into three types: linear, concave upward, and concave downward. The PS/PVME blend is a good example in which all three trends have been observed using different casting solvents.[12,13] When cast from chlorobenzene, toluene, and THF, I_D/I_M exhibits linear, concave-upward and concave-downward curvature with guest concentration, respectively. The blends prepared with toluene have been shown to be miscible for all proportions of PS and PVME, while blends prepared with THF have been shown to be immiscible. It appears that, in general, miscible blends are characterized by a concave-upward trend in I_D/I_M, and the reverse holds true for immiscible blends. The linear behavior is a limiting case for both types of blends.

For a miscible blend, the EFS concentration and the EET efficiency change slowly as the guest concentration is increased. From Figures 3–5, we observe the effects of changing the EET efficiency in sampling EFS on the curvature of I_D/I_M with guest concentration. We realize that the GF three-dimensional EET model should only be applied to blends with high guest concentration. Therefore, the extension of the GF model to low guest concentration assumes that the local EFS population is high enough to allow three-dimensional EET to occur. This may be valid for a system of isolated, tightly contracted guest coils dispersed in a poor host matrix. The GF model does not take into account any intramolecular morphological transformation as the guest concentration is increased. We merely intend to assess the qualitative behavior of I_D/I_M as a function of guest concentration for a miscible blend as the population and types of EFS are altered.

Figure 3 illustrates linear behavior in I_D/I_M for a system in which there is no intermolecular EFS formation. As the guest concentration increases, the EET process switches from mainly three-dimensional sampling of intramolecular EFS at low concentration to include sampling of intramolecular EFS on nearby chains at high concentration, i.e., cross-chain hopping. I_D/I_M continues to increase due to this enhanced sampling of intramolecular EFS by the exciton. The slope of the linear I_D/I_M trace depends on the population of the intramolecular EFS per chain.

It is unrealistic for blends with vinyl aromatic polymer to have no intermolecular EFS at high guest concentration. It is conceivable, however, that specific interactions between the guest polymer and the host or residual solvent in the film could yield a protective clustering around the chromophores, thereby lowering the probability of intermolecular EFS formation. Figure 4 illustrates the effect of introducing a small population of intermolecular EFS on the behavior of I_D/I_M. The I_D/I_M trace adopts a concave-upward curvature, especially for higher guest concentration. In addition to the enhanced sampling by three-dimensional EET, there are now more EFS to trap the excitation. The effect of increasing the probability of intermolecular EFS formation for a system with a fixed intramolecular EFS population is shown in Figure 5. In this figure, the transition from linear to concave-upward behavior is more dramatic with a higher probability of forming intermolecular EFS. It is important

to remember that each plot in Figures 3–5 represents systems in which the type and population of each type of EFS are held constant throughout the entire composition range. Our results for the P2VN/PCMA blend system in Figure 1 clearly show a combination of both linear and concave-upward I_D/I_M behavior due to changing EFS type and population with increasing P2VN concentration.

Polymer blends typically show a decrease in miscibility with increasing temperature. Whether a blend phase separates as part of the diffusive relaxation upon annealing depends on the annealing temperature relative to both the lower critical solution temperature and the glass transition temperature, respectively. For blends of P2VN and PCMA with molecular weights of 71 000 and 35 000, respectively, the annealing temperature of 413 K is probably below the lower critical solution temperature such that the blends remain miscible after annealing. Further annealing at 413 K allows the blend to relax into its equilibrium morphology while maintaining miscibility. The behavior of I_D/I_M, as shown in Figure 1, remains concave upward after annealing.

Gashgari and Frank[23] examined 71 000 M_v P2VN blended with PnBMA and PMMA. For the P2VN/PnBMA blend I_D/I_M increased with annealing at 407 K and leveled off after 25 h, while for P2VN/PMMA, I_D/I_M did not level off even after 160 h of annealing at 407 K. In both cases, I_D/I_M exhibited a concave-downward curvature as a function of P2VN bulk concentration. An explanation for the behavior of I_D/I_M as a function of annealing time in these different host matrices is due to thermally induced phase separation in the P2VN/PnBMA and P2VN/PMMA blends. These blends started out as optically cloudy films and remained cloudy after annealing. The increase in I_D/I_M can be due to an increase in the intermolecular EFS as a result of phase separation or an increase in the nonadjacent intramolecular EFS due to tightening of the polymer coils. The latter is more likely to happen with the P2VN/PMMA blend since it is a thermodynamically less compatible blend compared to P2VN/PnBMA.

In addition to the above two cases, the behavior of I_D/I_M with guest concentration for PS cast with THF in PVME has been observed to change from an initially concave-downward curvature to a concave-upward profile upon annealing. In this system, the appearance of phase separation is caused by possible kinetic limitations to the attainment of thermodynamic equilibrium, which in turn is due to the influence of residual casting solvent on the morphology of the blend. Zin and Frank[22] annealed PS/PVME blends cast with THF, which was earlier found to be phase separated, and observed a decrease in I_D/I_M back to values found for miscible PS/PVME blends cast from toluene.

The aggregation of chromophores during phase separation leads to a rapid increase in the population of both intermolecular and nonadjacent intramolecular EFS and favors three-dimensional EET among the chromophores. Overall, I_D/I_M increases rapidly for small changes in guest concentration and is reflected by a concave-downward behavior. As the P2VN bulk concentration increases, the P2VN-rich domains grow larger but with little change in the EFS population within the phase. Therefore, I_D/I_M levels out to the neat film value at high guest concentrations.

Gelles and Frank[12,13] have used excimer fluorescence as a molecular probe to determine the morphology and phase concentrations of phase-separated systems such as PS/PVME blends cast from THF. In deriving a two-phase model of I_D/I_M for phase-separated blends, they assumed that the volume fractions of the guest in the rich and lean phases, ϕ_R and ϕ_L, are independent of the bulk concentration ϕ_B. They further assumed that there will be no energy migration between phases. This is a good assumption because the guest chains in the lean phase should be sufficiently isolated so that the probability of three-dimensional EET is small, while the excitation in the rich phase should be rapidly trapped due to the high concentration within a concentrated phase that is large enough to scatter light. The problem then is reduced to first determining what fraction of photons is absorbed by each phase and then characterizing the deactivation pathway of an absorbed photon by a phase of known composition.

The resulting expression for I_D/I_M for a phase-separated blend is given by

$$\frac{I_D}{I_M} = \frac{Q_D}{Q_M}\frac{X_R(1-M_R)+(1-X_R)(1-M_L)}{X_R M_R+(1-X_R)M_L} \tag{10}$$

where X_R is the probability that a photon is absorbed by a ring in the rich phase and is given by

$$X_R = \frac{\phi_R(\phi_B-\phi_L)}{\phi_R(\phi_B-\phi_L)+\phi_L(\phi_R-\phi_B)} \tag{11}$$

The quantities M_R and M_L are the probabilities of eventual excitation deactivation through a monomer pathway for an absorbed photon originating in the guest-rich and guest-lean phases, respectively. To use eq 10, we must obtain estimates for ϕ_R and ϕ_L at the casting temperature from a phase diagram for the blend, and M_R and M_L are determined from the fluorescence data for miscible blends of the same components using eq 2.

Since we require photophysical information from a miscible system to estimate M_R and M_L, we need to investigate the influence of M derived from a miscible blend on the behavior of I_D/I_M for phase-separated blends. The significant qualitative feature is that M usually decreases rapidly with increasing guest concentration. This is a consequence of the increase in the number of EFS traps and the expected increase in efficiency of EET due to increased dimensionality of the random walk. The combination of these two effects leads to considerable nonlinearity.

For miscible blends exhibiting a linear, quadratic, or cubic dependence of M on ϕ_B (i.e., the profile of M derived from the behavior of I_D/I_M on ϕ_B using eq 2), it can be shown that eq 10 assumes the form

$$\frac{I_D}{I_M} = \frac{A+B\phi_B}{C+\phi_B} \tag{12}$$

where the constants A, B, and C represent different algebraic relations between the quantities ϕ_R, ϕ_L, and Q_D/Q_M. We will illustrate the derivation of eq 12 for a linear dependence of M on ϕ_B. It is a straightforward exercise for other functional forms of M on ϕ_B.

For a miscible system exhibiting a linear dependence of I_D/I_M on ϕ_B

$$I_D/I_M = \alpha' + \beta'\phi_B \tag{13}$$

the parameters M_R and M_L assume the following form according to eq 2;

$$M_R = (\alpha+\beta\phi_R)^{-1} \tag{14}$$

$$M_L = (\alpha+\beta\phi_L)^{-1} \tag{15}$$

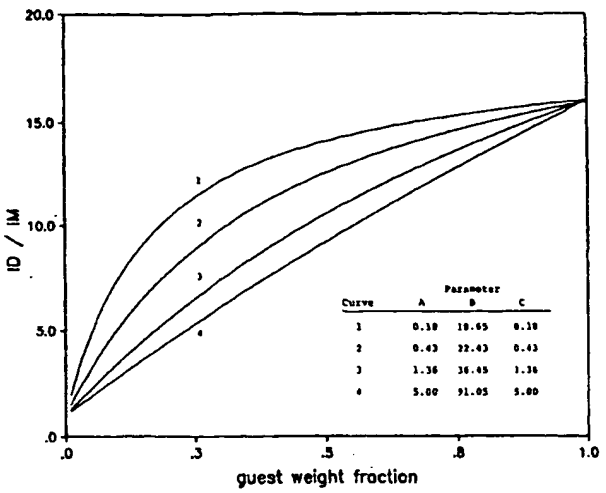

Figure 8. Behavior of I_D/I_M as a function of bulk guest concentration for a phase-separated blend. The concave-downward curves follow the GF two-phase model as described in eq 10–12.

where the constants $\alpha = (\alpha' + Q_D/Q_M)/(Q_D/Q_M)$ and $\beta = \beta'/(Q_D/Q_M)$. Substituting eq 11, 14, and 15 into eq 10 and collecting the terms into the form of eq 12, we find the following forms for the constants A, B, and C:

$$A = \frac{\phi_R\phi_L\{\alpha^2 - \beta\phi_R - \alpha\beta\phi_L - \beta^2\phi_R\phi_L\}}{(\phi_R - \phi_L)(1 + \alpha)} \quad (16)$$

$$B = \frac{(\phi_R - \phi_L)\alpha(1 + \alpha) + \phi_R{}^2\{\beta(1 + \alpha) + \beta^2\phi_L\}}{(\phi_R - \phi_L)(1 + \alpha)} \quad (17)$$

$$C = \frac{\beta\phi_R\phi_L}{1 + \alpha} \quad (18)$$

Using the phase-separated PS/PVME blend cast from THF as an example, we find the quantities ϕ_R, ϕ_L, α, and β have values of 0.98, 0.008, 1.0, and 10, respectively. The behavior of eq 12 as a function of guest concentration for typical values of A, B, and C is shown in Figure 8. The concave-downward trend seems to be intrinsic for phase-separated blends.

V. Summary

First, we have shown for low molecular weight P2VN/PCMA blends that solvent casting with toluene at room temperature and subsequent evaporation by air-drying lead to a nonequilibrium blend morphology. The latter is characterized by a high population of both intermolecular and intramolecular EFS, which upon annealing at 413 K, approach the equilibrium statistical population. The photostationary-state fluorescence results for blends with P2VN concentration above 50 wt % are well characterized by a three-dimensional EET model. The effective lifetime for monomer deactivation supports the hypothesis that near 50 wt %, the mode of EET becomes three-dimensional, thereby increasing the trapping by EFS.

Second, although the blends remain optically clear after annealing for 96 h at 413 K, there might be local phase separation for blends with higher guest concentration above 70 wt %. These guest-rich domains are probably small enough not to scatter light or be detected by conventional methods such as DSC.

Finally, the behavior of I_D/I_M as a function of guest concentration is distinctly different for miscible and immiscible blends. The curvature of I_D/I_M with increasing guest concentration may be used as a first-order fingerprint characterization for blend miscibility.

Acknowledgment. This work was supported by the Polymers Program of the National Science Foundation under Grant DMR 84-07847.

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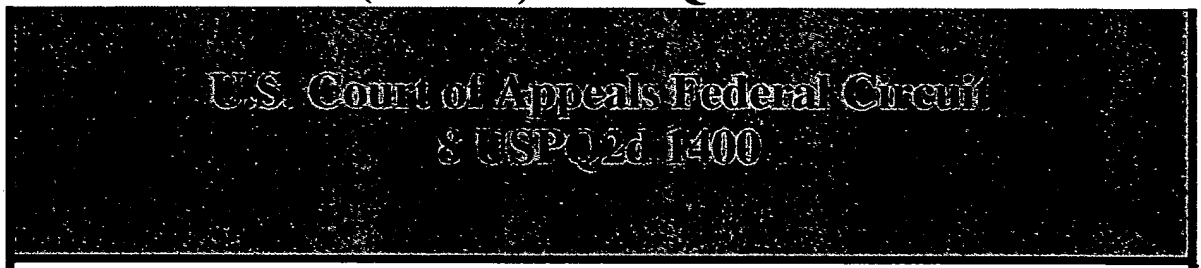

Decided September 30, 1988
No. 87-1454

Headnotes

PATENTS

1. Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Data disclosed in application for immunoassay method patent, which shows that applicants screened nine of 143 cell lines developed for production of antibody necessary to practice invention, stored remainder of said cell lines, and found that four out of nine cell lines screened produced antibody falling within limitation of claims, were erroneously interpreted by Board of Patent Appeals and Interferences as failing to meet disclosure requirements of 35 USC 112, since board's characterization of stored cell lines as "failures" demonstrating unreliability of applicants' methods was improper in view of fact that such unscreened cell lines prove nothing concerning probability of success of person skilled in art attempting to obtain requisite antibodies using applicants' methods.

2. Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Disclosure in application for immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring "undue experimentation," even though production of monoclonal antibodies necessary to practice invention first requires

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production and screening of numerous antibody producing cells or "hybridomas," since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one "experiment" is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Case History and Disposition:

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent of Jack R. Wands, Vincent R. Zurawski, Jr., and Hubert J. P. Schoemaker, serial number 188,735. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicants appeal. Reversed; Newman, J., concurring in part and dissenting in part in separate opinion.

Attorneys:

Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein (Henry N. Wixon, with them on brief), Washington, D.C., for appellant.

John H. Raubitschek, associate solicitor (Joseph F. Nakamura and Fred E. McKelvey, with him on brief), PTO, for appellee.

Judge:

Before Smith, Newman, and Bissell, circuit judges.

Opinion Text

Opinion By:

Smith, J.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims

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in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM

Antibodies," which was filed September 19, 1980. 1 The rejection under 35 U.S.C. §112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

I. *Issue*

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. §112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. *Background*

A. *The Art*.

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an antigen. The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure of an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests (*e.g* ., to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay* .

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes* . Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from

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serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. There are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.
The blood cells that make antibodies are *lymphocytes* . Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.
Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma

cells that are all progeny of a single cell) are called monoclonal antibodies. 2

B. *The Claimed Invention* .

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. §112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.
The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could

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be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25-27 are for chemically modified (*e.g* ., radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
determining the presence of said substance in said sample;
wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^{9}M^{-1}$.

Certain claims were rejected under 35 U.S.C. §103; these rejections have not been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25-27 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. *Analysis*

A. *Enablement by Deposit of Micro-organisms and Cell Lines .*

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention." 3 A patent need not disclose what is well known in the art. 4 Although we review underlying facts found by the board under a "clearly erroneous" standard, 5 we review enablement as a question of law. 6

Where an invention depends on the use of living materials such as microorganisms or

cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. 7 Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. 8 A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. 9 Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials. 10

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In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention, 11 and to satisfy the requirement under 35 U.S.C. §114 that the PTO be guaranteed access to the invention during pendency of the application. 12 Although a deposit may serve these purposes, we recognized, in *In re Lundak* , 13 that these purposes, nevertheless, may be met in ways other than by making a deposit.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. *Undue Experimentation* .

Although inventions involving microorganisms or other living cells often can be enabled by a deposit, 14 a deposit is not always necessary to satisfy the enablement requirement. 15 No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. 16 Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case. 17

Appellants contend that their written specification fully enables the practice of

their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980. 18 The sole issue is whether, in this particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies.

Enablement is not precluded by the necessity for some experimentation such as routine screening. 19 However, experimentation needed to practice the invention must not be undue experimentation. 20 "the key word is 'undue,' not 'experimentation.' " 21

The determination of what constitutes undue experimentation in a given case requires the

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application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), *cert. denied* , 404 U.S. 1018 [172 USPQ 257] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * * . 22

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. 23 Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* . 24 They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. 25

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medi

um in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest. Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not

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yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least $10^{9}M^{-1}$. 26 The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

During prosecution Wands submitted a declaration under 37 C.F.R §1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that 27 It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (Ka [greater than] $10^{9}M^{-1}$) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion). fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least $10^{9}M^{-1}$. Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. §1.56 that applicants fully disclose all of their relevant data, and not just favorable results. 28 How these stored hybridomas are viewed is central to the positions of the parties.

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least $10^{9}M^{-1}$. Thus, only 4 out of 143 hybridomas, or 2.8 percent, were *proved* to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to

engage in undue experimentation in order to make antibodies that fall within the claims.

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Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least $10^{9}M^{-1}$. Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. §1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

[1] We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable. 29 At worst, they prove nothing at all about the probability of success, and merely show that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

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[2] When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that un

due experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure. 30

IV. *Conclusion*

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. §112, first paragraph, is reversed.

REVERSED

Footnotes

Footnote 1. *In re Wands* , Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).
Footnote 2. For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc* ., 802 F.2d 1367, 1368-71, 231 USPQ 81, 82-83 (Fed. Cir. 1986), *cert. denied* , 107 S.Ct. 1606 (1987).
Footnote 3. *W.L. Gore & Assocs., Inc. v. Garlock, Inc* ., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 851 (1984).

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Footnote 4. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co .*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).
Footnote 5. *Coleman v. Dines* , 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).
Footnote 6. *Moleculon Research Corp. v. CBS, Inc .*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), *cert. denied* , 107 S.Ct. 875 (1987); *Raytheon Co. v. Roper Corp .*, 724 F.2d 951, 960 n.6, 220 USPQ 592 , 599 n.6 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 835 [225 USPQ 232] (1984).
Footnote 7. *In re Argoudelis* , 434 F.2d 1390, 1392-93, 168 USPQ 99, 101-02 (CCPA 1970).
Footnote 8. *In re Lundak* , 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); *Feldman v. Aunstrup* , 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied* , 424 U.S. 912 [188 USPQ 720] (1976); Manual of Patent Examining Procedure (MPEP) 608.01 (p)(C) (5th ed. 1983, rev. 1987). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement* , 67 J. Pat. Trademark Off. Soc'y 569 (1985).
Footnote 9. *In re Jackson* , 217 USPQ 804, 807-08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman* , 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis* , 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp* , 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).
Footnote 10. *Ex parte Forman* , 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak* , 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).
Footnote 11. *In re Lundak* , 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman* , 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis* , 434 F.2d at 1394-96, 168 USPQ at 103-04 (Baldwin, J. concurring).
Footnote 12. *In re Lundak* , 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman* , 517 F.2d at 1354, 186 USPQ at 112.
Footnote 13. *In re Lundak* , 773 F.2d at 1222, 227 USPQ at 95-96.
Footnote 14. *In re Argoudelis* , 434 F.2d at 1393, 168 USPQ at 102.
Footnote 15. *Tabuchi v. Nubel* , 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).
Footnote 16. *Id* . at 1186-87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co .*, 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J. 1967); *Guaranty Trust Co. v. Union Solvents Corp .*, 54 F.2d 400, 403-06, 12 USPQ 47, 50-53 (D. Del. 1931), *aff'd* , 61 F.2d 1041, 15 USPQ 237 (3d Cir. 1932), *cert. denied* , 288 U.S. 614 (1933); MPEP 608.01 (p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").
Footnote 17. *In re Jackson* , 217 USPQ at 807; *see In re Metcalfe* , 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).
Footnote 18. *Hybritech* , 802 F.2d at 1384, 231 USPQ at 94.
Footnote 19. *Id.; Atlas Powder Co. v. E.I. DuPont De Nemours & Co .*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); *In re Angstadt* , 537 F.2d at 502-504, 190 USPQ at 218; *In re Geerdes* , 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Mineral Separation, Ltd. v. Hyde* , 242 U.S. 261, 270-71 (1916).
Footnote 20. *Hybritech* , 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore* , 721 F.2d at

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1557, 220 USPQ at 316; *In re Colianni* , 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).
Footnote 21. *In re Angstadt* , 537 F.2d at 504, 190 USPQ at 219.
Footnote 22. *In re Jackson* , 217 USPQ at 807.
Footnote 23. *See Hybritech* , 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder* , 750 F.2d at 1576, 224 USPQ at 413.
Footnote 24. *Ex parte Forman* , 230 USPQ at 547.
Footnote 25. *Id.; see In re Colianni* , 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer* , 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).
Footnote 26. The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as *avidity* , which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high-affinity" as essentially synonymous with "having a binding affinity constant of at least $10^{9}M^{-1}$."
Footnote 27. A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than $10^{9}M^{-1}$.
Footnote 28. *See Rohm & Haas Co. v. Crystal Chem. Co* ., 722 F.2d 1556, 220 USPQ 98 (Fed. Cir. 1983).
Footnote 29. Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.
Footnote 30. *In re Strahilevitz* , 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

Concurring/Dissenting Opinion Text

Concurrence/Dissent By:

Newman, J., concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.
Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are

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relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc* ., 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied* , 107 S.Ct. 1606 (1987). I agree that it is not necessary that there be a deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. §112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:
19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least $10^{9}M^{-1}$.
26. Monoclonal high affinity IgM antibodies immunoreactive with hepatitis B surface antigen.
Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.
Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)
Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experi

ments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman* , 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).
The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. §112. *In re Fisher* , 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).
As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law

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and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. *See* , *e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc* ., 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 851 (1984); *In re Angstadt* , 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook* , 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover* , 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer* , 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman* , 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

- End of Case -

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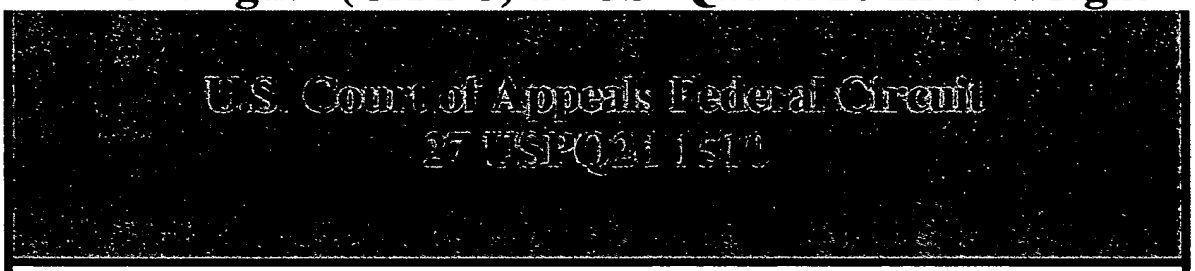

Decided July 20, 1993
No. 92-1437

Headnotes

PATENTS

1. Patentability/Validity -- Specification -- Enablement (§ 115.1105)

JUDICIAL PRACTICE AND PROCEDURE

Procedure -- Judicial review -- Standard of review -- Patents (§ 410.4607.09)

Statutory requirement of enablement is question of law that is reviewed de novo on appeal, but any underlying facts found by Board of Patent Appeals and Interferences in rendering its enablement determination will be reviewed for clear error.

2. Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office, in rejecting claim under enablement requirement of 35 USC 112, bears initial burden of setting forth reasonable explanation of why scope of

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protection provided by claim is not adequately enabled by specification's description of invention, and this burden includes providing sufficient reasons for doubting any assertions in specification as to scope of enablement; if PTO meets this burden, then burden shifts to applicant to provide suitable proofs indicating that specification is enabling.

3. Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office set forth reasonable basis for its finding that scope of claims directed to producing live, non-pathogenic vaccines against pathogenic RNA viruses is not enabled by specification's general description, which contained only single working example directed to uniquely tailored in vitro method of producing particular recombinant virus vaccine, and applicant has failed to rebut this finding by demonstrating how skilled artisan in February 1983 would have been able, without undue experimentation, to carry out identification, isolation, cloning, recombination, and efficacy testing steps required to practice full scope of claims; applicant has also failed to show that claims, even if restricted to vaccines against avian tumor viruses, are enabled, since he has failed to establish that scientist at that time would have reasonably believed that applicant's success with particular strain of avian RNA virus could be extrapolated with reasonable expectation of success to other avian RNA viruses.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent, serial no. 06/914,620, filed by Stephen E. Wright. From board's decision sustaining examiner's rejection of claims, applicant appeals. Affirmed.

Attorneys:

Peter M. Peer, of Mallinckrodt & Mallinckrodt (Philip A. Mallinckrodt, with him on brief), Salt Lake City, Utah, for appellants.

Teddy S. Gron, associate solicitor (Fred E. McKelvey, solicitor, with him on brief; Richard E. Schafer, John W. Dewhirst, Albin F. Drost, and Lee E. Barrett, of counsel), for PTO.

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Judge:

Before Rich, Newman, and Rader, circuit judges.

Opinion Text

Opinion By:

Rich, J.

Dr. Stephen E. Wright appeals from the January 16, 1992 decision of the Board of Patent Appeals and Interferences (Board) of the United States Patent and Trademark Office (PTO) sustaining the Examiner's rejection of claims 1-23, 15-42, and 45-48 of application Serial No. 06/914,620 1 under 35 USC Section 112, first paragraph, as unsupported by an enabling disclosure.2 We affirm.

I. BACKGROUND

A. *The Invention*

The claims on appeal are directed to processes for producing live, non-pathogenic

vaccines against pathogenic RNA viruses (claims 1-10, 22-37, 40, 45, and 46), vaccines produced by these processes (claims 11, 12, 15-21, 38, and 39), and methods of using certain of these claimed vaccines to protect living organisms against RNA viruses (claims 41 and 42). Wright's specification provides a general description of these processes, vaccines, and methods of use, but only a single working example.

In this example, Wright describes the production of a recombinant vaccine which confers immunity in chickens against the RNA tumor virus known as Prague Avian Sarcoma Virus (PrASV), a member of the Rous Associated Virus (RAV) family. To produce this vaccine, Wright first identified the antigenic gene region of the genome of PrASV as being in the envelope A (*env* A) gene region of this virus, and then isolated and cloned a large quantity of this antigenic gene region. Following cloning, Wright introduced by transfection the cloned *env* A genes into C/O cells, a particular chicken embryo cell line. The C/O cells were then infected with the endogenous, non-oncogenic, O-type Rous Associated Virus (RAV-O) and incubated. Genetic recombination and viral replication occurred during incubation, resulting in an impure vaccine containing particles of the recombinant virus referred to as RAV-O Acn, or RAV-O-A. 3 Wright then purified this vaccine to obtain a vaccine containing only genetic recombinant RAV-Acn virus particles. The Examiner ultimately allowed claims 13, 14, 43, and 44, which are specific to the particular process and vaccine disclosed in this example.4

Wright seeks allowance, however, of claims which would provide, in varying degrees, a much broader scope of protection than the allowed claims. For example, independent process claim 1 reads:

A process for producing a live non-pathogenic vaccine for a pathogenic RNA virus, comprising the steps of identifying the antigenic and pathogenic gene regions of said

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virus; performing gene alteration to produce a genome which codes for the antigenicity of the virus, but does not have its pathogenicity; and obtaining an expression of the gene. Dependent claims 2-10, 22-35, and 40 recite additional limitations to this process. Independent claims 36 and 45 and claims 37 and 46 dependent therefrom, respectively, are also directed to processes for producing vaccines.

Independent product claim 11 reads:

A live, non-pathogenic vaccine for a pathogenic RNA virus, comprising an immunologically effective amount of a viral antigenic, genomic expression having an antigenic determinant region of the RNA virus, but no pathogenic properties.

Dependent claims 15-21 recite additional limitations to this vaccine. Independent claims 38 and 47 and claims 39 and 48 dependent therefrom, respectively, are also directed to vaccines.

Dependent claims 41 and 42 recite methods of protecting living organisms against RNA viruses, which comprise introducing into a host an immunologically effective amount of the vaccine of claims 11 and 38, respectively.

B. *The Rejection*

The Examiner took the position in her Examiner's Answer that the claims presently on appeal are not supported by an enabling disclosure because one of ordinary skill in the art would have had to engage in undue experimentation in February of 1983 (the effective filing date of Wright's application) to practice the subject matter of these claims, given their breadth, the unpredictability in the art, and the limited guidance Wright provides in his application. The Examiner noted that many of Wright's claims read on vaccines against *all* pathogenic RNA viruses, even though RNA viruses are a very diverse and genetically complex group of

viruses which include, among others, acquired immunodeficiency syndrome (AIDS) viruses, leukemia viruses, and sarcoma viruses. The Examiner argued that Wright's single working example merely evidenced that Wright had obtained successfully a particular recombinant virus vaccine, and that this single success did not provide "sufficient likelihood" that other recombinant RNA viruses could be constructed without undue experimentation, or if they were constructed, that they would be useful in the design of like viral vaccines. The Examiner noted the inability of the scientific community to develop an efficacious AIDS virus vaccine for humans despite devoting a considerable amount of time and money to do so.

The Examiner further argued that, even though retroviruses as a class may exhibit similar gene order and possess envelope proteins, this alone does not support a general conclusion that all RNA virus envelope proteins will confer protection against the corresponding virus. The Examiner asserted that this held true even among avian RNA tumor viruses. At page 11 of her Answer, the Examiner stated that "one envelope gene's immunogenicity cannot be extrapolated to another envelope gene. The efficacy of each should be ascertained individually."

To support the foregoing, the Examiner relied upon an article by Thomas J. Matthews et al., *Prospects for Development of a Vaccine Against HIV*, in Human Retroviruses, Cancer, and AIDS: Approaches to Prevention and Therapy 313-25 (1988). This article

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indicates that AIDS retroviruses, which represent only a subset of all RNA viruses, were known even as late as 1988 to show great genetic diversity, including divergent virus envelopes. It further indicates that, although AIDS retroviruses elicited strong immune responses in goats and chimps in 1988, the resulting antibodies did not prevent retrovirus infectivity. Moreover, this article also recognizes at page 321 that, as of 1988, animal models for HIV infection and disease were likely to be imperfect, and therefore testing of primary vaccine candidates in man was necessary to determine safety, immunogenicity and efficacy.

Finally, the Examiner also argued that, irrespective of immunogenicity and vaccine considerations, the methods of identification, isolation, cloning, and recombination which Wright describes in his application in only a very general manner were not so developed in 1983 as to enable, without undue experimentation, the design and production of recombinant virus vaccines against any and all RNA viruses. The Examiner also asserted that the considerable amount of time and effort that it took Wright to construct the particular avian recombinant virus described in his single working example and to establish its efficacy as a vaccinating agent illustrates the amount of undue experimentation that would have been required in February of 1983 to practice Wright's invention, especially given that the efficacy of the developed virus could not be extrapolated with any certainty to other recombinant viruses at that time.

C. *The Board Decision*

In its January 16, 1992 decision, 5 the Board held that the Examiner did not err in questioning the enablement of the physiological activity required by the appealed claims, given the breadth of these claims and the fact that a vaccine must by definition provoke an immunoprotective response upon administration. The Board found that Wright had failed to establish that the general description of his invention set forth in his application was anything more, in February of 1983, than an invitation to experiment. The Board agreed with the Examiner that this general description does not set forth such sufficient detailed guidance that one of ordinary skill in the art would have had any reasonable expectation of success in constructing other vaccines against other RNA viruses. The Board additionally noted that the Examiner only allowed the claims limited to Wright's single working example after Wright submitted *in vivo* evidence of the efficacy of this vaccine.

The Board further held that the record did not support Wright's arguments that this single working example enables some of his dependent claims which are closer in scope to the allowed claims than to independent claims 1 and 11. The Board found that, even if Wright was correct in stating that it was generally known that an "immune response" is assured by use of an antigenic envelope protein, the record did not establish that such an "immune response" would have been an immunoprotective one, or moreover, that one skilled in this art would have expected such a result in February of 1983. The Board relied upon the Matthews et al. article as evidencing that "the mere use of an envelope protein gene in the present invention is not seen to necessarily result in the obtention of successful vaccines throughout the scope of

even these more limited claims." Bd. Dec. at 6.

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As to Wright's request that the Board consider several declarations and exhibits of record, the Board stated that it found no reason to consider this evidence with any particularity since Wright had failed to advance any specific arguments based on this evidence or to explain its relevance.

II. DISCUSSION A.

[1] The first paragraph of 35 USC Section 112 requires that the specification of a patent contain a written description of the claimed invention and the manner and process of making and using that invention in such full, clear, concise, and exact terms as to enable any person skilled in the art to which that invention pertains, or with which it is most nearly connected, to make and use that invention. As a statutory requirement, enablement is a question of law that we review de novo; however, we review for clear error any underlying facts found by the Board in rendering its enablement determination. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

[2] When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling. *Marzocchi*, 439 F.2d at 223-24, 169 USPQ at 369-70.

B.

In the present case, the PTO set forth a reasonable basis for finding that the scope of the appealed claims is not enabled by the general description and the single working example in the specification. Consequently, the burden shifted to Wright to present persuasive arguments, supported by suitable proofs where necessary, that the appealed claims are truly enabled. Wright failed to meet this burden.

Both the Examiner and the Board correctly pointed out that Wright's appealed claims are directed to vaccines, and methods of making and using these vaccines, which must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough. 6 Both also correctly pointed out that Wright attempts to claim in many of the appealed claims *any and all* live, non-pathogenic vaccines, and processes for making such vaccines, which elicit immunoprotective activity in *any* animal toward

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any RNA virus. In addition, both properly stressed that many of the appealed claims encompass vaccines against AIDS viruses and that, because of the high degree of genetic, antigenic variations in such viruses, no one has yet, years after his invention, developed a generally successful AIDS virus vaccine.
The Matthews et al. article, published approximately 5 years after the effective filing date of Wright's application, adequately supports the Examiner's and the Board's position that, in February of 1983, the physiological activity of RNA viruses was sufficiently unpredictable that Wright's success in developing his specific avian recombinant virus vaccine would not have led one of ordinary skill in the art to believe reasonably

that all living organisms could be immunized against infection by any pathogenic RNA virus by inoculating them with a live virus containing the antigenic code but not the pathogenic code of the RNA virus. The general description and the single example in Wright's specification, directed to a uniquely tailored *in vitro* method of producing in chicken C/O cells a vaccine against the PrASV avian tumor virus containing live RAV-Acn virus particles, did nothing more in February of 1983 than invite experimentation to determine whether other vaccines having *in vivo* immunoprotective activity could be constructed for other RNA viruses.
Wright argues that he has constructed successfully an *env* C recombinant vaccine according to the present invention and that certain recombinant AIDS virus vaccines carrying SIV (simian immunodeficiency virus) and HIV (human immunodeficiency virus) envelope genes have been produced which confer protective immunity in the animal models where they have been tested, 7 and that these developments illustrate that the art is not so unpredictable as to require undue experimentation. However, all of these developments occurred after the effective filing date of Wright's application and are of no significance regarding what one skilled in the art believed as of that date. 8 Furthermore, the fact that a few vaccines have been developed since the filing of Wright's application certainly does not by itself rebut the PTO's assertions regarding undue experimentation. Moreover, whether a few AIDS virus vaccines have been developed which confer immunity in some animal models is not the issue. The Examiner made reference to the difficulty that the scientific community is having in developing generally successful AIDS virus vaccines merely to illustrate that the art is not even today as predictable as Wright has suggested that it was back in 1983.
Wright also argues that several affidavits of record, namely, an October 22, 1984 declaration by Wright, an October 23, 1984 affidavit by O'Neill, and October 28, 1988 affidavits by Bennett and Burnett, successfully rebut the Board's and the Examiner's assertions regarding undue experimentation. However, Wright did not set forth in his brief to the Board any specific arguments regarding these affidavits, as required by 37 CFR 1.192(a), and therefore we are not required to address the arguments that Wright presents in this appeal regarding these affidavits. *Chester v. Miller*, 906 F.2d 1574, 1578 n.6, 15 USPQ2d 1333, 1337 n.6 (Fed. Cir. 1990); *In re Wiseman*, 596 F.2d 1019, 1022, 201 USPQ 658, 661 (CCPA 1979).
[3] Nevertheless, we note that each of these affidavits fails in its purpose because each merely contains unsupported conclusory statements as to the ultimate legal question. 9

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See In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);

In re Brandstadter, 484 F.2d 1395, 1405-06, 179 USPQ 286, 293-94 (CCPA 1973). Furthermore, Burnett and Bennett do not even indicate in their affidavits that they actually reviewed the specification of Wright's application. In addition, although Wright states in his declaration that the individual steps making up his claimed process were "well within the skill of the art" at the time that he filed his application and makes reference to a list of publications that he contends supports this conclusory statement, a list which Wright also makes reference to in his arguments to this court, Wright fails to point out with any particularity in this declaration, or in his arguments to this court, how the listed documents evidence that a skilled artisan in February of 1983 would have been able to carry out, without undue experimentation, the identification, isolation, cloning, recombination, and efficacy testing steps required to practice the full scope of the appealed claims.

C.

Wright further argues that, even if those claims which provide a broad scope of protection are not enabled, this is not the case as to those claims restricted to vaccines against avian tumor viruses. Wright maintains that there is no doubt that it was known in 1983 that the technique of producing a live vaccine proven effective for one particular strain of avian RNA viruses would be effective as to other strains of avian RNA viruses. Wright argues that the scientific literature supports the position that the art was predictable at least with respect to avian RNA viruses, because gene function and order are similar among all avian RNA viruses.

We are not persuaded. Wright has failed to establish by evidence or arguments that, in February of 1983, a skilled scientist would have believed reasonably that Wright's success with a particular strain of an avian RNA virus could be extrapolated with a reasonable expectation of success to other avian RNA viruses. Indeed, Wright has failed to point out with any particularity the scientific literature existing in February of 1983 that supports his position. Furthermore, Wright's May 17, 1989 declaration indicates that Wright himself believed during the relevant time period that *in vivo* testing was necessary to determine the efficacy of vaccines. In this declaration, Wright stated in pertinent part:

Preparation of a patent application following conception of the invention awaited such time as there was a reasonable expectation that the results of innoculation [sic] would be successful. *This became apparent only by reason of survival of the chickens that had been innoculated* [sic].

Wright now argues that all he meant by the foregoing was that *in vivo* efficacy testing was necessary for the first avian RNA viruses vaccine that he developed in order to prove his hypothesis. Wright asserts that, once his hypothesis had been proven, a skilled artisan would have expected that similar *in vivo* results could be obtained for vaccines developed for other avian retroviruses. However, a paper that Wright co-authored with David Bennett, titled "Avian Retroviral Recombinant Expressing Foreign Envelope Delays Tumor Formation of ASV-A-Induced Sarcoma," which was attached to a

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declaration by Wright dated November 19, 1985, suggests that, even as late as 1985, the genetic diversity existing among chickens alone required efficacy testing even among the members of this narrow group. 10 Accordingly, we see no error in the Board's finding that one skilled in the art would not have believed as early as February of 1983 that the success of Wright's one example could be extrapolated with a reasonable expectation of success to all avian RNA viruses.

D.

Finally, Wright argues that each of the appealed claims should be considered independently to determine whether it satisfies the enablement requirement of section 112. This we have done. Wright's arguments to this court, however, are directed almost entirely to why he believes that the specification of his application enables the appealed claims as a whole or at least those claims limited to avian RNA viruses. Although Wright does refer in passing to each of the appealed claims, he does little more than recite the particular limitations recited in these claims, failing to point out how the enablement requirement is satisfied as to each of these claims independently. Consequently, Wright has failed to provide us with any justification for finding that the Board erred in sustaining the Examiner's rejection, even with respect to some of the more limited claims.

CONCLUSION

For the foregoing reasons, the decision of the Board is affirmed.
AFFIRMED

Footnotes

Footnote 1. Application Serial No. 06/914,620, filed on October 2, 1986, is a continuation of Serial No. 06/469,985, filed February 25, 1983, now abandoned.
Footnote 2. In an April 12, 1992 reconsideration decision, the Board denied Wright's request that it modify its original decision.
Footnote 3. Transfection, infection, genetic recombination, and viral replication collectively constitute a procedure known as marker rescue.
Footnote 4. The allowed claims read:

Claim 13 A live, non-pathogenic vaccine for a pathogenic RNA virus, comprising an immunologically effective amount of a viral, antigenic, genomic expression having an antigenic determinant region of the RNA virus, but no pathogenic properties, the viral, antigenic, genomic expression being the RAV-Acn virus.

Claim 14 A vaccine according to claim 13, wherein the vaccine has been purified by selection for the expression of the antigenic genome.

Claim 43 A process for producing a live, non-pathogenic, recombinant vaccine

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conferring immunity against the PrASV avian tumor virus in chickens, comprising inserting the PrASV env A gene into a RAV-O virus by marker rescue such that said PrASV env A gene replaces the endogenous envelope gene of the RAV-O virus; and selecting for the recombinant in C/E cells.

Claim 44 A live, non-pathogenic, recombinant vaccine conferring immunity against the PrASV avian tumor virus in chickens, in which vaccine the PrASV env A gene has been inserted into a RAV-O virus by marker rescue to replace the endogenous envelope gene of the RAV-O virus, and the recombinant has been selected for in C/E cells.

Footnote 5. The Board stated in its opinion that it was affirming the Examiner's rejection under section 112 for the reasons set forth in the Examiner's Answer and that the Board's added comments were for emphasis only.

Footnote 6. Wright defines "vaccine" at page 1 of his specification as being a "material which induces an organism to acquire immunity against disease." Furthermore, as noted by the Board, the *Dictionary of Biochemistry* 330 (John Wiley & Sons 1975), defines "vaccine" as a suspension of antigens derived from viruses or bacteria that, upon administration, will produce active immunity and provide protection against those viruses or bacteria or related viruses or bacteria.

Footnote 7. *See* Shio-Luk Hu et al., *Protection of Macaques Against SIV Infection by Subunit Vaccines of SIV Envelope Glycoprotein gp160,* 255 Science 456-59 (1992); Shio-Luk Hu et al., *Neutralizing Antibodies Against HIV-1 BRU and SF2 Isolates Generated in Mice Immunized with Recombinant Vaccinia Virus Expressing HIV-1 (BRU) Envelope Glycoproteins and Boosted with Homologous gp 160,* 7 AIDS RESEARCH AND HUMAN RETROVIRUSES 616-20 (1991); Phillip W. Berman et al., *Protection of Chimpanzees from Infection by HIV-1 after Vaccination with Recombinant Glycoprotein gp120 but not gp160,* 345 Nature 622-625 (1990).

Footnote 8. In his appeal to this court, Wright all too frequently slips into using the present tense to discuss the state of the art and what a skilled artisan would believe given Wright's success with one avian virus. We note, however, that the issue is not what the state of the art is today or what a skilled artisan today would believe, but rather what the state of the art was in February of 1983 and what a skilled artisan would have believed at that time. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir.), *cert denied,* 480 U.S. 947 (1987); *In re Hogan,* 559 F.2d 595, 604, 194 USPQ 527, 535 (CCPA 1977). Wright's tendency to employ the present tense often makes it difficult to determine whether Wright is asserting that certain information was known prior to February of 1983 or simply that that information is now known in the art.

Footnote 9. For example, O'Neill stated in his affidavit that the specification provided him "with sufficient information to produce a vaccine for any known pathogen in accordance with the procedural steps claimed" and that he could not "foresee any problem in producing similar vaccines for other pathogens." Bennett and Burnett merely declared in their affidavits that, at the time they worked with Wright, they believed that the specific vaccine that they were developing was simply one example within a broader concept. In his October 22, 1984 declaration, Wright stated that he knew "of no reason why the specific vaccine tested is not truly indicative of successful application of other embodiments of the invention within the purview of the teachings and claims of my patent application." Wright further stated that " [although the project has been primarily

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directed toward the production and testing of a specific vaccine for a specific virus, the concept has been inherently generic as claimed."
Footnote 10. The paper states in pertinent part: "Recent observations suggest line SC chickens do not respond well immunologically. . . . Follow up experiments will include other chicken lines. Mechanisms of protection are also under study."

- End of Case -

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